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FULMINATING BACILLUS COLI SEPTICEMIA IN WOMEN WITH DIABETES

REPORT OF FOUR CASES, WITH SPECIAL REFERENCE TO CLINICAL DIAGNOSIS

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In September 1938 an obese woman with diabetes was admitted to the Buffalo General Hospital in a stuporous state, from which she gradually lapsed into unconsciousness. She presented a clinical picture such as we had not seen before. High fever and leukocytosis were present, and the only apparent cause for this was that suggested by the finding of pus and bacteria in the urine. The patient had been acutely ill for only a day. Treatment was directed toward the diabetes, but she lived only three days. No diagnosis was made until the blood culture, which was taken soon after admission, showed a pure growth of Bacillus coli.

Within a period of less than a year 3 more patients presented a clinical picture so similar to that of the first patient that the diagnosis was readily suggested, and treatment was instituted before the blood cultures had yielded growth. These 4 cases are presented to call attention to the similarity and dissimilarity between the symptoms of the disease to be described and those of diabetic coma. Further, we wish to stress the importance of an early diagnosis of this apparently fulminating form of Bacillus coli septicemia in women with diabetes if chemotherapy is to be attempted.

REPORT OF CASES

CASE 1.—Mrs. Z., aged 63, was admitted to the Buffalo General Hospital Sept. 22, 1938 and died on September 25. She was known to have had diabetes

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for three years. A diet and insulin were prescribed by her physician, but neither counsel was obeyed. She had been up and around the house until the day before admission, when she suddenly complained of "being cold." She went to bed, and drowsiness soon ensued.

Examination showed a rather stout woman in a state of restless stupor. Her face was flushed, and her rectal temperature was 104 F. Her breathing was rapid and irregular but not of the Kussmaul type. Her pulse was rapid and bounding; the blood pressure was 210 systolic and 110 diastolic. Her lungs were clear except for rales heard at the base of the right lung posteriorly, where there was a slight prolongation of expiration. The abdomen was normal except that the liver was palpable a few centimeters below the costal margin. There was no evidence of meningeal irritation or of paralysis.

The urine was cloudy and had a specific gravity of 1.022. It gave an acid reaction. It contained albumin (3 plus) and sugar (3 plus). When tested with sodium nitroprusside, it gave a 1 plus reaction. There was sediment to a depth of 2 mm. in the centrifuge tube after spinning, composed entirely of leukocytes, mostly clumped, and bacteria.

The blood contained 400 mg. of dextrose and 37 mg. of urea nitrogen per hundred cubic centimeters. The carbon dioxide capacity of the plasma was 50 volumes per cent. The red cells numbered 4,250,000; the hemoglobin value was 80 per cent, and the white blood cell count was 24,000 with 88 per cent polymorphonuclears, of which 12 per cent were young forms. The spinal fluid was clear and under a pressure of 144 mm. of water. There was but a trace of protein, and the copper reduction was prompt. The colloidal gold curve and the Wassermann reaction were negative. A catheterized specimen of urine showed many white blood cells and gram-negative rods in the smear. The culture showed B. coli. The blood culture taken two days after admission also revealed B. coli; but these were not identified until after the patient's death.

Course.—On admission the patient was treated with insulin, physiologic solution of sodium chloride parenterally and dextrose as well as fluids given by mouth. The stupor increased so rapidly that within twenty-four hours she could no longer be aroused.

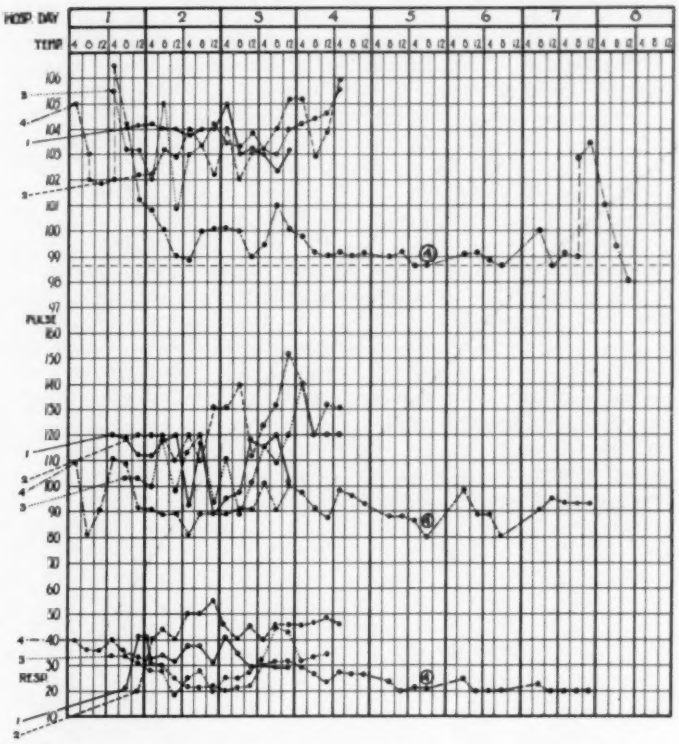
Necropsy (Dr. K. Terplan).—There was marked interstitial pyelonephritis, especially of the left kidney, with multiple bilateral pinhead abscesses, mostly on the under surfaces of the capsules. The smear showed gram-negative rods. Moderate cystitis and ureteritis were present, particularly on the left. The spleen was septic and weighed 500 Gm.; the splenic culture showed B. coli. There was eccentric hypertrophy of the heart with atherosclerosis of the arch of the aorta and of the coronary arteries. The pancreas weighed 70 Gm. Histologic section of the kidneys showed arteriolar nephrosclerosis with persistence of the embryonal lobulations.

Case 2.—Mrs. G., aged 54, was brought to the Buffalo General Hospital in coma on Nov. 19, 1938 and died three days later. The history was obtained from the family. The patient had been treated in the hospital two years previously and was discharged with prescription of insulin and a diet. She took the insulin for two weeks and was said to have observed the diet for a year. Two days before the second admission nausea and vomiting developed, and she became more and more drowsy.

Examination on admission showed a comatose obese woman. Her rectal temperature was 102.5 F.; the pulse rate was 120; the respirations were 40 per minute

and shallow. The blood pressure, taken on two occasions, was 126 systolic and 86 diastolic and 134 systolic and 80 diastolic. There were none of the clinical signs of dehydration.

The urine was cloudy, and the specific gravity was 1.024. It gave a 3 plus reaction for albumin, and a negative reaction for ferric chloride. There was sediment of 5 mm. in the bottom of the centrifuge tube, made up almost entirely of white blood cells and motile bacteria. The blood dextrose was 888 mg. per hundred cubic centimeters. The carbon dioxide capacity of the plasma was 60



Composite chart showing temperatures, pulse rates and respiration rates of 4 patients with fulminating B. coli septicemia.

volumes per cent. The spinal fluid was clear, with 6 white blood cells per cubic millimeter, no increase of protein and prompt copper reduction. The red blood cells numbered 4,000,000; the hemoglobin value was 82 per cent; white blood cells were 18,300 with 75 per cent filamentous and 17 per cent young forms. The Wassermann reaction was negative. The blood culture which was taken on her second hospital day showed 60 colonies of B. coli per cubic centimeter; they, however, were not identified until after the patient's death.

Course.—At first the patient was treated for diabetic coma with fluids parenterally and large amounts of insulin. There was no change in her condition. The day following admission she was given 500 cc. of an 0.8 per cent solution of sulfanilamide subcutaneously. This was repeated the next day. The urea nitrogen content of the blood was not ascertained on the day of admission, but on the second day in the hospital it was 90 mg. per hundred cubic centimeters. On the day of her death it was 102 mg. The sulfanilamide in the blood reached a level of 19 mg. the day before her death. At that time the carbon dioxide capacity of the plasma was found to have dropped to 38 volumes per cent, possibly as a result of the administration of sulfanilamide. There was no autopsy.

Case 3.—Mrs. W., aged 69, was admitted to the Buffalo General Hospital on July 1, 1939 and died July 4. She was seen by one of us (B. D. B.) in consultation with Dr. Philip Goldstein. It was known that she had had diabetes since 1920. Left hemiplegia occurred in October 1937; from this she recovered. During May 1939 a pain developed in the region of the left hip. About June 1 she had an attack of frequency, urgency and burning of urination; her urine at that time was cloudy. She was treated with sulfanilamide and improved. Before admission to the hospital she had been receiving 20 units of insulin daily. On June 29 a chill developed; her temperature rose to 104 F., and restlessness ensued.

Examination at the hospital showed an obese woman in a state of restlessness and mental confusion. She frequently dozed for short intervals, even during conversation. Her rectal temperature was 105.6 F. Her respirations were rapid and rather deep. There was no clinical evidence of dehydration. A few coarse rales were heard in the right scapular region. The blood pressure was 136 systolic and 78 diastolic. The pulse rate was 112. No explanation was found for the fever on physical examination.

The urine was cloudy; its specific gravity was 1.021. It had an acid reaction. It contained albumin (3 plus) and sugar (3 plus). It gave a 1 plus reaction to the sodium nitroprusside and a negative reaction to the ferric chloride test. The sediment, 0.5 mm. in a 15 cc. centrifuge tube after spinning, was entirely leukocytes and bacteria. The direct smear of the catheterized specimen showed many leukocytes and gram-positive cocci in chains and a few gram-negative rods. The culture was B. coli and enterococci. The blood sugar was 460 mg., urea nitrogen 20 mg., per hundred cubic centimeters. The carbon dioxide capacity of the plasma was 47 volumes per cent. The red blood cells numbered 3,800,000 per cubic millimeter; the hemoglobin value was 80 per cent. The white blood cells numbered 14,800 with 95 per cent polymorphonuclears, 25 per cent of which were band forms. The blood culture taken on admission showed 8 colonies per cubic centimeter. These were not identified until just before the patient's death; another culture taken after she had sulfanilamide showed 10 colonies of B. coli per cubic centimeter.

Course.—During the first twenty-four hours she was able to take a small amount of food and fluids by mouth. She received only 26 units of insulin during the first twenty-four hours; during this period 4 Gm. of sulfanilamide and 2.5 of sodium bicarbonate were also given. The following day she was considerably worse and would not take anything by mouth. During the next two days she received physiologic solution of sodium chloride and 5 per cent dextrose intravenously and 40 to 50 units of insulin with each 1,000 cc. On July 3 and 4 she

received a total of 160 cc. of azosulfamide[1] intramuscularly in doses of 20 cc. She did not become absolutely comatose until twenty-four hours before death. There was no autopsy.

CASE 4.—Mrs. B., aged 63, was admitted to the Buffalo General Hospital on July 25, 1939 and discharged on Aug. 6, 1939. She was seen in consultation with Dr. Robert Ullman by one of us (B. D. B.). She had symptoms of diabetes for only a year, during which time her weight decreased from 220 to 205 pounds (99.8 to 93 Kg.). The diabetes had not been treated. The patient dated her acute illness from July 7, 1939, when she noted drowsiness, easy fatigability and frequency and burning of urination. There had also been some loss of appetite and nausea. Her doctor, called just prior to her admission, observed fever.

At the hospital, examination showed an obese woman. Her rectal temperature was 104 F. There was no clinical evidence of dehydration. The patient answered questions readily, but it was difficult to obtain data from her because she had a tendency to drop off to sleep as soon as conversation ceased. The respirations were rapid and deep and were described by the house officer as being of the Kussmaul type. The heart was slightly enlarged, and there was a soft systolic murmur at the apex, which was transmitted over the entire precordium. The blood pressure was 186 systolic and 80 diastolic. There was no evidence of disturbance of the central nervous system.

The urine showed a trace of albumin, contained sugar (4 plus) and gave a 1 plus sodium nitroprusside reaction. The sediment, 2 mm. in a 15 cc. centrifuge tube after spinning, was composed of leukocytes and bacteria. The red cells numbered 4,200,000 per cubic millimeter, and the hemoglobin value was 83 per cent. The white blood cells numbered 14,400; 78 per cent of these were polymorphonuclears; 38 per cent, young forms; 2 per cent, eosinophils; 16 per cent, lymphocytes, and 4 per cent, monocytes. The blood sugar on admission was 512 mg., urea nitrogen, 14 mg., per hundred cubic centimeters. The carbon dioxide capacity of the plasma was 55 volumes per cent. The culture of the urine showed B. coli, Bacillus aerogenes capsulatus and enterococci. The blood culture showed B. aerogenes capsulatus, 50 colonies per cubic centimeter.

Course.—The patient was not able to be dieted but took a limited amount of fruit juices by mouth. These were supplanted, however, with physiologic solution of sodium chloride and 5 per cent dextrose solution intravenously, with 30 to 40 units of insulin preceding each clysis of 1,000 cc. She was treated with sulfanilamide twelve hours after admission; she received 3 Gm. during the first twenty-four hours. On the second day she had a chill, and her rectal temperature rose to 106.5 F. Then dosage of sulfapyridine, 1 Gm. every four hours, was started and continued throughout her illness; during the next twelve days she received 60 Gm. by mouth. Her rectal temperature on the next two days rose only to 100 and 101 F., respectively, following the chills.

After her temperature had been normal for three days, she was again catheterized. This was followed by a sharp chill; the temperature rose to 104 F., but immediately receded and did not rise again.

The specimen of urine taken on July 29 still showed many leukocytes and contained B. aerogenes capsulatus and enterococci. The white blood cell count con-

1. Azosulfamide is disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

tinued to be high and on August 5 was 18,000 with a considerable shift to the left. The blood culture became negative. When the patient was discharged, however, the urine still contained gram-negative rods and gram-positive cocci, which on culture proved to be B. aerogenes capsulatus and enterococci. The diabetes was controlled with a diet of 100 Gm. of carbohydrate, 80 Gm. of protein and 100 Gm. of fat with 50 units of regular insulin daily.

One year after discharge she was receiving 34 units of insulin, and the diabetes was well controlled. The urine was free from pus and bacteria, and the leukocytosis had disappeared.

COMMENT

Septicemia caused by B. coli, according to Davis and Turner,[2] has been reported in the literature in 110 instances in the past fifty years. Presumably many such cases go undiagnosed because of failure to make blood cultures or to make them at the time when bacteremia is present. The mortality rate as observed by a number of authors varies from 30 to 40 per cent, depending somewhat on the source of the infection. Textbook descriptions of septicemia due to B. coli indicate that there is no characteristic clinical picture. This may be said of most septicemias. It is well known that fulminating septicemia due to any organisms may be associated with delirium, stupor and, finally, coma. However, septicemia due to B. coli is not ordinarily regarded as an acute fulminating disease, except as an agonal event.

In our cases the patients were struck down with an acute illness, usually with a sudden chill, at a time when they did not regard themselves as ill enough to seek medical attention. From then on the course was rapid. The duration of the disease was from four to five days with the exception of the 1 patient who recovered. The blood cultures were taken either at admission to the hospital or within thirty-six hours. The characteristic clinical picture present in all 4 cases was drowsiness which rather rapidly became coma. Two of the patients manifested narcoleptic phenomena; only 1 showed definite delirium. It seems obvious that sulfanilamide was without effect in 2 of the patients at the stage of the disease at which it was used. In case 3 an effort was made to obtain sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) for intravenous use, but the material did not arrive until the patient had died. In case 4 the patient, who had B. aerogenes capsulatus in both the blood stream and the urine, was treated with sulfapyridine rather early in the disease, and it is reasonable to assume that the treatment was effective.

It is possible that fulminating septicemia due to B. coli or related organisms occurs more frequently in patients with uncontrolled diabetes

2. Davis, N. P., and Turner, O. E.: Colon Bacillus Septicemia Associated with Calculus Obstruction of the Common Duct: Review of Literature and Report of Case, Pennsylvania M. J. **43**:26-28 (Oct.) 1939.

and infection of the urinary tract. In our patients the dextrose concentrations in the blood varied between 400 and 800 mg. per hundred cubic centimeters, almost optimal conditions for the growth of gram-negative bacilli. Kutzman and one of us (B. D. B.[3]) made a complete urologic survey of 84 unselected cases of diabetes occurring in women between the ages of 36 and 79. We observed B. coli or closely related organisms in the ureteral urine either by direct smear or culture in 34 of the cases. Sharkey and Root [4] likewise called attention to the frequency of B. coli infections in the urinary tracts of persons with diabetes.

In considering the problem of immunity Richardson [5] compared the bactericidal power of the blood for B. coli of persons with diabetes with that of normal persons. He noted that the blood of persons with diabetes was but slightly weaker than his normal controls in killing power for that organism. It is conjectured that a sudden invasion of the blood stream occurs in the person with uncontrolled diabetes who has urinary infections. Because large amounts of dextrose are present, multiplication of the organism in the blood stream might occur much more rapidly than in the blood of normal persons, especially if the bactericidal power of the blood serum is impaired.

SUMMARY AND CONCLUSIONS

Four cases are reported in which the patients, all obese women with uncontrolled diabetes, had a fulminating form of septicemia caused by a gram-negative bacillus of the colon aerogenes group. In 3 cases B. coli (Escherichia coli) was grown from cultures of both the blood and the urine; in the remaining case similar cultures showed the B. aerogenes capsulatus (Aerobacter aerogenes).

The disease is characterized by an acute onset and a rapid course. It proved fatal with the exception of the 1 patient whose infection was caused by B. aerogenes capsulatus and who recovered after treatment with sulfapyridine.

No antemortem diagnosis was made in the first case because the organism found in the blood stream was not identified until after the patient's death. Necropsy revealed chronic pyelonephritis with small capsular abscesses. The clinical observations in the other 3 cases were

3. Bowen, B. D., and Kutzman, N.: The Urinary Tract in Diabetic Women: Its Contribution to the Incidence of Hypertension, Ann. Int. Med., to be published.

4. Sharkey, T. P., and Root, H. F.: Infection of the Urinary Tract in Diabetes, J. A. M. A. **104**:2231-2235 (June 22) 1935.

5. Richardson, R.: Immunity in Diabetes: Influence of Diabetes on the Development of Antibacterial Properties in the Blood, J. Clin. Investigation **12**: 1143 (Nov.) 1933.

so similar to those in the first case that the diagnosis was suggested and treatment begun before identification of the organism in the blood stream was possible.

The characteristic clinical manifestation was a drowsiness which rather rapidly passed into unconsciousness. Two of the patients manifested narcolepsy of a peculiar type.

Although 2 of the patients were regarded as having diabetic coma on admission and were treated for this condition, the facts that diabetic coma is not common in obese patients with diabetes, that these patients were not appreciably dehydrated and that they had high temperatures should have served to distinguish their disease from diabetic coma.

PULMONARY STENOSIS WITH BUNDLE BRANCH BLOCK

REPORT OF A CASE WITH SOUND TRACINGS AND SEMISERIAL STUDIES OF THE CONDUCTION BUNDLE

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The incorporation of the bulbus cordis into the definitive heart is so often imperfect that among cardiac anomalies defects in the outflow tract of the right ventricle are common. Occasionally, however, after the fundamental structures of the heart have been completed, stenosis of the pulmonary valve develops. This lesion, according to Abbott,[1] is "practically always inflammatory, the result of an endocarditis running its course late in foetal life." White [2] agreed that pulmonary stenosis is "almost invariably the result of congenital defects."

As already intimated, uncomplicated pulmonary stenosis is rare; in 1,000 cases of congenital heart disease studied statistically by Abbott only 9 cases were listed. Levine [3] stated in his chapter on congenital heart disease, "Pulmonary stenosis as an isolated lesion is quite rare." References to uncomplicated pulmonary stenosis associated with bundle branch block have not been found.

Bundle branch block has been the subject of much investigation during the past thirty years. In 1938 this work, of which an important part has been done in the United States, was summarized by Yater.[4] Emphasizing the scarcity of pathologic studies, he reported 16 cases

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Presented before the Fulton County Medical Society, June 20, 1940.

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Mr. M. B. Rappaport, of the Sanborn Company, recorded the sound tracings and interpreted them for us. Dr. Everett L. Bishop made the photomicrographs.

1. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936, p. 44.

2. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937, p. 455.

3. Levine S. A.: Clinical Heart Disease, ed. 2, Philadelphia, W. B. Saunders Company, 1940, p. 207.

4. Yater, W. M.: Pathogenesis of Bundle Branch Block: Review of the Literature; Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction System, Arch. Int. Med. **62**:1-96 (July) 1938.

with autopsies; in 11, serial sections of the conduction system had been studied histologically. Since 1938 Bischoff [5] has reported histologic studies of the conduction system in 4 cases, but he has not presented photomicrographs. Certain lines from Yater's admirable monograph may be quoted:

> The pathogenic factor in cases of bundle branch block is almost always disease of the coronary arteries, rheumatic or degenerative, or hypertension. . . . The histogenic factor . . . is mainly fibrosis. . . . The vascularization of the conduction system explains well why it is rare for one bundle branch alone to be affected.

In 1928 King [6] suggested that bundle branch block can often be recognized from physical signs. The most important of these was a bifid thrust of the apex. The auscultatory signs listed were feebleness of systolic heart sounds, reduplication of the first sound at the apex (including presystolic gallop) and asynchronous systolic apical murmurs. Although four of the first five diagnoses made by one of us (L. M. B.) were confirmed electrocardiographically, his subsequent experience has indicated that the percentage of clinical recognition of bundle branch block is no higher than is to be explained by the laws of chance. It is the present consensus that bundle branch block can be proved only by the electrocardiograph. It may be that exact study of the heart sounds will eventually increase the accuracy of clinical diagnosis. For such exact study, especially for demonstration, graphic records are necessary. Practical methods of recording the heart sounds synchronously with electrocardiographic deflections have but recently been introduced. The presentation of such records in a case of bundle branch block is thus worth while, even though in the present case the record is complicated by the effects of a pronounced valvular lesion.

Because pulmonary stenosis without other gross structural defects is rare; because sound tracings of hearts studied pathologically are still novelties; because few histologic studies of abnormal conduction bundles have been reported, and because an account presenting these three features in combination does not appear to have been published before, the following case is reported.

REPORT OF CASE

In the course of routine physical examination of college boys in September 1934, C. S., aged 18, was observed. Tall, but poorly nourished and poorly developed, he was of the vagotonic type with the subdued manner of a boy who has never been able to run and play and fight. He stated that he had suffered

5. Bischoff, S.: Vergleischende electrocardiographisch-histologische Studien an vier Fällen unter besonderer Berücksichtigung des Reizleitungssystems, Beitr. z. path. Anat. u. z. allg. Path. **103**:183-214, 1939.

6. King, J. T.: The Clinical Recognition and Physical Signs of Bundle Branch Block, Am. Heart J. **3**:505-524 (June) 1928.

from heart trouble since babyhood. The area of cardiac dulness was greatly enlarged. A systolic thrill was felt along the left border of the sternum, and a harsh systolic murmur was heard, loudest in the pulmonic region. The pulse pressure was low and the pulse rate rapid.

On Sept. 16, 1937, an opportunity was afforded for detailed study. His father had died of pneumonia at 54. His mother was in good health. She had suffered no infections during any of her 5 pregnancies; her 4 other children were living and well.

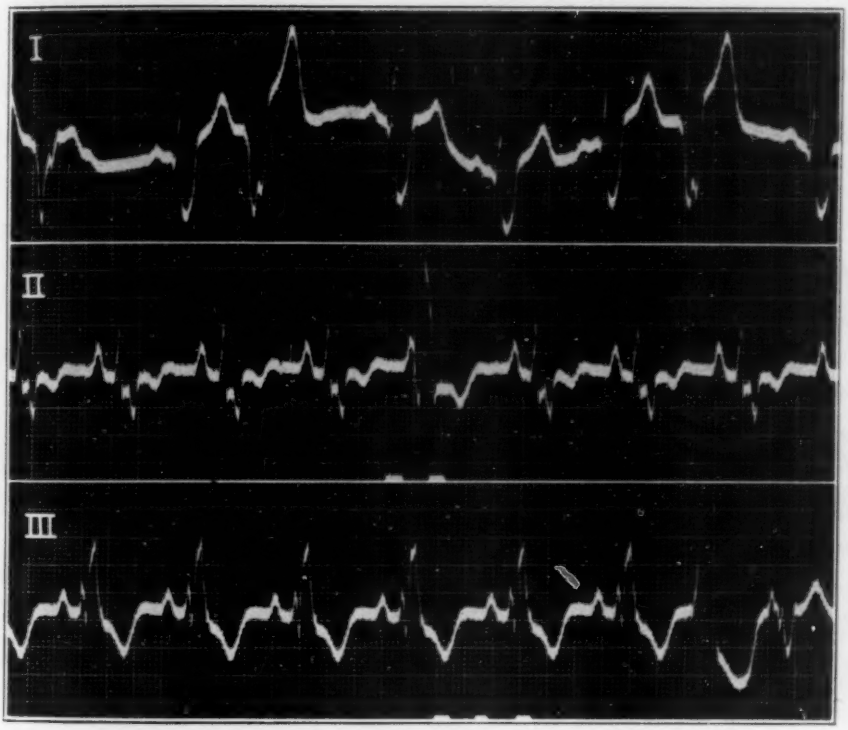

Fig. 1.—Electrocardiogram taken Oct. 7, 1937. The pulse rate is 80. QRS measures 0.18 second. In addition to the right bundle branch block, the electrocardiogram shows 6 premature ventricular contractions, most of which arose in the right ventricle.

C. S. had been delivered uneventfully and was considered a normal baby until an illness at 2, an ailment characterized by fever and difficulty in swallowing. Soon after this a heart murmur was noted for the first time; it was attributed to the recent illness. As a child he could "play catch," but he was not able to run after a ball or engage in more strenuous games. By the time he entered high school, his physical activities were greatly limited, and whatever he did, he had to do slowly. When he entered college, difficulty in going upstairs influenced

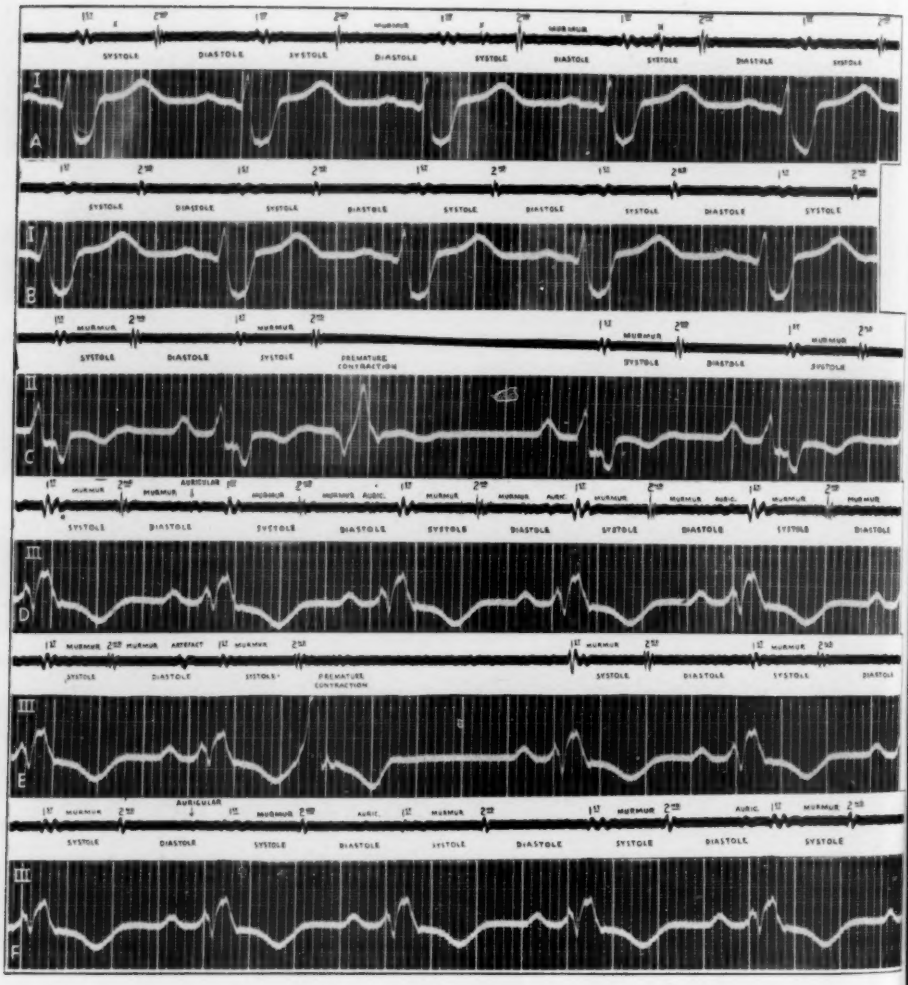

Figure 2

(See legend on opposite page)

his choice of courses. He had, however, been able to work his way through by means of sedentary jobs, especially tutoring. Although he could not walk a block slowly without stopping to rest, he had never noted edema. Cyanosis had not been observed at rest. He had been singularly free of infectious diseases.

At the 1937 examination, C. S. was 72½ inches (184 cm.) tall and weighed 130 pounds (59 Kg.). He was faintly cyanotic; his hands were clammy; the fingers were slightly clubbed. The neck veins collapsed in diastole. The precordium bulged, and there was a diffuse heaving beat. Cardiac dulness extended out into the axilla, and a systolic thrill was felt along the left border of the sternum. Heart action was irregular. A harsh systolic murmur was heard in the pulmonic region. The blood pressure at rest was usually about 114 systolic

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EXPLANATION OF FIGURE 2

A, lead I with the bell in the fourth interspace 5 cm. from the midline. There are a low-pitched first heart sound and a higher-pitched second sound, and a very slight systolic murmur. About midway in systole there is an extra heart sound of variable intensity (x), possibly a systolic gallop. There is also a variable diastolic murmur (lead I).

B, bell in fifth interspace of the anterior axillary line. The first sound is of very low pitch (probably below human audibility); the second is higher pitched and somewhat more intense (lead I).

C, bell at third interspace just to the left of the sternum. There are a fairly low-pitched first heart sound and a somewhat higher-pitched, more intense second sound, and a slight systolic murmur. At the time of the occurrence of the premature contraction no heart sound occurs. A possible reason for the lack of a heart sound during the premature contraction may be that it preceded the time the atrioventricular valves were sufficiently open; that is, the presence of a first heart sound depends on the closure of a previously opened atrioventricular valve. Similiarly, the second sound depends on the closure of the previously opened semilunar valves. If the semilunar valves do not open owing to the premature ventricular contraction, the absence of a second heart sound is to be expected (lead II).

D, bell at first left interspace. A low-pitched first heart sound is present, followed by a systolic murmur. The systolic murmur has a tendency to become more intense later in systole but covers practically all of the systolic phase. A second sound of much higher pitch is present, followed by a short diastolic murmur. Also present is an auricular sound, well displaced and prior to the first heart sound. A rather interesting point concerning the systolic and diastolic murmurs is that the major frequency components are the same in both murmurs; the systolic murmur appears to run through the second heart sound to form the diastolic murmur (lead III).

E, bell at second right interspace. There are a very low-pitched first heart sound, a slight systolic murmur, a second heart sound of higher pitch and a very low-pitched rumble (well below the range of human audibility) throughout diastole. A premature contraction accompanied by a slight heart sound is also present (lead III).

F, bell just below the sternoclavicular joint. There are very low-pitched first and second sounds, a medium high-pitched systolic murmur and, trailing the second sound, a soft diastolic murmur (lead III).

and 96 diastolic; the pulse rate was 80. Slight exertion might change the blood pressure to 136 systolic and 76 diastolic and the pulse rate to 120.

Fluoroscopic examination showed a huge heart with enlargement principally to the left and backward. In view of the physical signs of obstruction in the outflow tract of the right ventricle it was thought that this ventricle probably formed the apex. The aorta appeared normal. The pulmonary trunk was greatly dilated.

The electrocardiogram showed right bundle branch block (Bayley's [7] group 1) and frequent premature ventricular contractions, arising principally in the right ventricle.

He was graduated in June, 1938. During the following year the requirement of a physical examination several times barred him from professional employment. Although he picked up occasional temporary jobs, especially in tutoring, he grew discouraged and profoundly depressed. He fainted several times and several times feared he would faint, apparently owing to paroxysms of tachycardia.

On April 4, 1939, Mr. M. B. Rappaport recorded the heart sounds synchronously with an electrocardiogram. His interpretations are presented in the legends of the illustrations. In brief, the sound tracings corroborated the presence of a systolic murmur, loudest in the pulmonic area and followed by a short diastolic murmur heard only there.

Six weeks after these records were made, C. S. left home apparently as well as ever. Half an hour later he was found dead in his car. He had pulled up to the curb, cut off the ignition, pocketed the keys and opened the door.

Necropsy.—The postmortem examination (the cranium was not opened) revealed little of interest except in the heart. This organ extended to the left wall of the thorax and almost to the posterior wall; it had crowded the left lung into the upper part of the thoracic cavity. The heart weighed 955 Gm. (according to Smith,[8] the average weight of the heart of a man of 130 pounds [59 Kg.] is 255 Gm.). The right ventricle formed practically the anterior surface of the heart (fig. 3) and indeed the greater mass of the heart. From the apex to the level of the pulmonary ring the heart measured 15 cm., and across the base, 14 cm. The anteroposterior diameter was 11 cm. The thickness of the wall of the right ventricle in some places was 4 cm.; the average thickness of the left was 1.8 cm. The tricuspid ring showed some dilatation, measuring 12.5 cm. in circumference; the leaflets were moderately thickened, but appeared to have been functionally adequate. The pulmonary valve was a tough dome-shaped membrane, measuring around its base about 8.5 cm.; in its upper surface was a circular aperture 6 mm. in diameter. Viewed from above (as shown in the inset of fig. 3) three ridges represented fusion of the commissures between the three semilunar cusps. The pulmonary trunk was dilated and thin walled; its inner circumference was 12.5 cm. The mitral valve measured 10 cm.; its leaflets were slightly thickened. The normal aortic valve was 6 cm. in inner circumference. The coronary ostiums were not obstructed.

The fundamental structure of the heart was normal; there was no anomalous communication between the two sides of the heart. The right atrium was markedly

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7. Bayley, R. H.: The Frequency and Significance of Right Bundle Branch Block, Am. J. M. Sc. **188**:236-242 (Aug.) 1934.

8. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body, and of the Weight of the Heart to Age, Am. Heart J. **4**:79-93 (Oct.) 1928.

dilated. The right ventricle was even more dilated, especially in the pulmonary conus. This great enlargement of the right chambers resulted in a torsion of the heart with displacement of the interventricular septum backward and to the left. This displacement was so great that a needle passed through the septum at the base of the posterior and lateral aortic leaflets entered the right atrium about 4 cm. posterior to the pars membranosa septi rather than through this structure itself. Grossly, the myocardium evidenced a high degree of fibrosis.

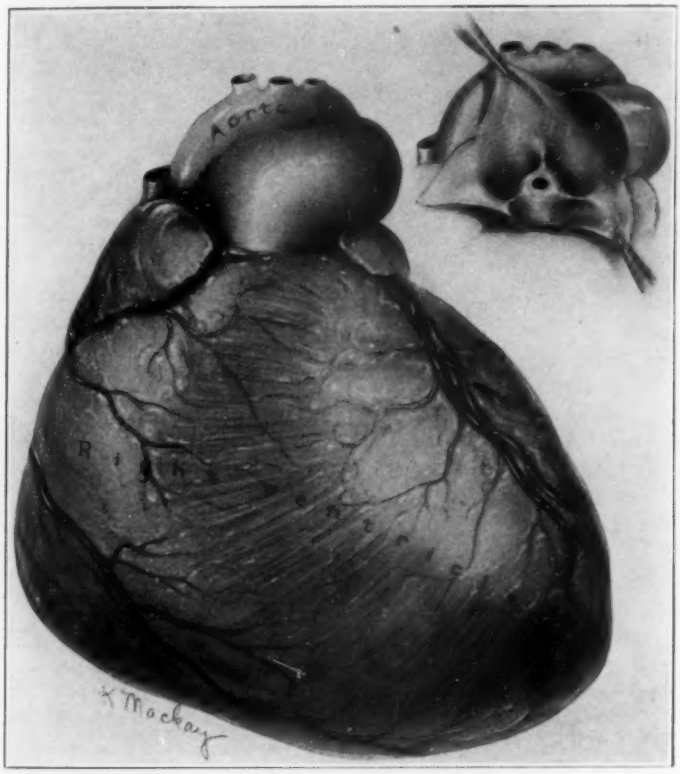

Fig. 3.—The appearance of the heart. Note the size of the right ventricle and how it forms the apex of the heart. Note also the dilated pulmonary trunk. The inset shows the appearance of the pulmonary valve from above: it is apparent that three semilunar cusps were formed and that they later fused.

Histologic Studies.—Tissue from the lower part of the interatrial septum extending down toward the interventricular septum and including the pars membranosa was removed and cut into 3 equal blocks. Microscopic sections were taken from each block at intervals of approximately 60 microns to show the conduction bundle longitudinally (see fig. 4 *A*).

A number of the sections showed the main bundle throughout most of its length down to the point where it divided just above the pars membranosa. Microscopic evidence of considerable damage was present. Variation in the staining of the

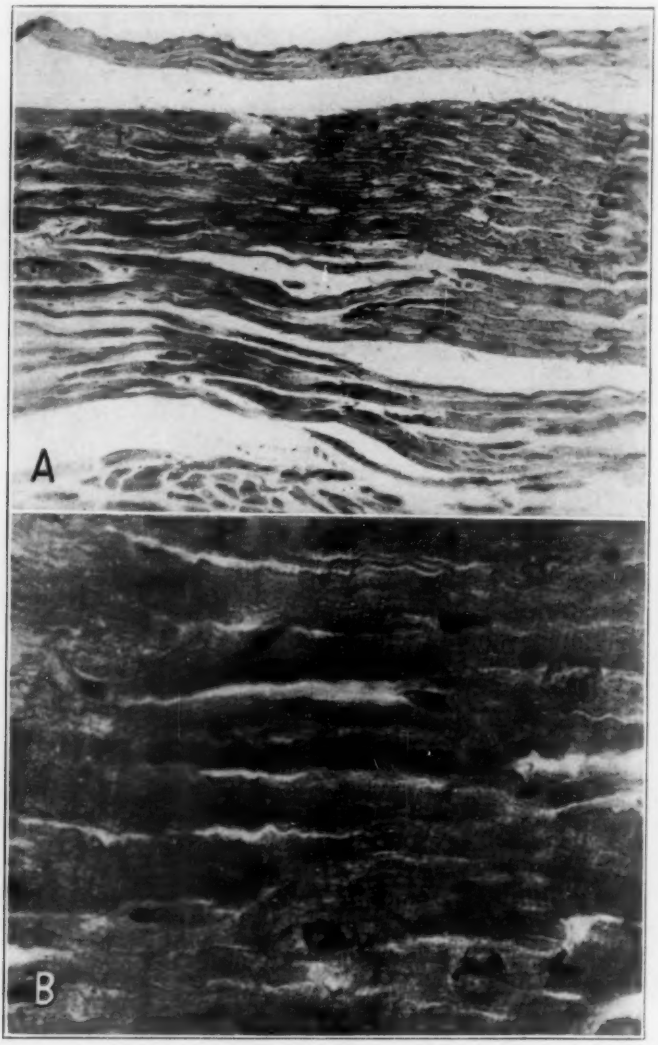

Fig. 4.—*A*, low power photomicrograph showing a longitudinal section of the main conduction bundle immediately proximal to the pars membranosa. Hematoxylin and eosin stain; × 150. *B*, higher power photomicrograph of a part of *A* showing light-staining areas of granular degeneration and dark homogeneous areas resembling Zenker's hyalin. Hematoxylin and eosin stain; × 600.

muscle fibers gave the tissue a mottled appearance. The darker areas exhibited a loss of striation, causing a homogeneous appearance suggestive of Zenker's hyaline degeneration. The lightly stained portions showed definite granulation

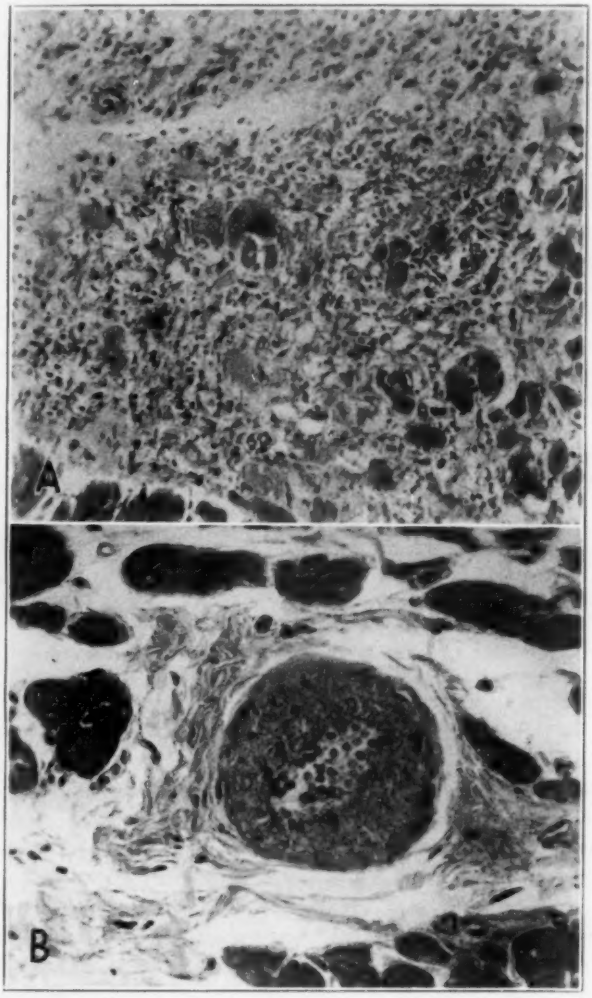

Fig. 5.—*A*, low power photomicrograph showing an area of ischemic necrosis in the upper part of the interventricular septum. There is complete destruction of the myocardium with chronic inflammatory and fibroblastic reaction. Hematoxylin and eosin stain; × 150. *B*, high power photomicrograph of an artery in the upper part of the interventricular septum. The lumen is narrowed by subintimal proliferation. The dark spots throughout the vessel wall are pigment deposits. Hematoxylin and eosin stain; × 600.

(fig. 4 *B*). There was also variation in size and staining character of the nuclei; some were markedly pyknotic. No actual replacement of the bundle by fibrous tissue could be demonstrated. These changes were most pronounced in the portion of the bundle just proximal to its bifurcation at the pars membranosa. The amount of damage to the tissue in the muscle bundle appeared sufficient to cause the defect of conduction.

In sections from other parts of the heart, particularly in those from the upper part of the interventricular septum, the cardiac muscle showed diffuse fibrosis. This fibrosis had resulted in loss of muscle tissue and definite abnormality of that which remained. In some areas inflammatory infiltration, mainly by mononuclear and large phagocytic cells but with a few eosinophils, was noted (fig. 5 *A*). In one place there was a distinct foreign body giant cell reaction. These lesions showed none of the characteristics of a tuberculous reaction, nor were they the type seen in the Aschoff body. The appearance was more that of active regeneration of fibrous tissue in an area of destroyed cardiac muscle.

The arteries showed thickening of the walls with subintimal proliferation and narrowing of the lumen. Heavy deposition of brown granular material, apparently blood pigment, was seen in the arterial walls (fig. 5 *B*).

COMMENT

Abbott's [1] account of congenital pulmonary stenosis might have been written to describe the case of C. S.:

> In these uncomplicated cases the right ventricle is always the seat of a marked simple hypertrophy and the right auricle dilated, but the heart is otherwise normal. . . . Such cases are much less frequent than the developmental type of pulmonary stenosis with associated ventricular septal defect and dextroposition of the aorta, but the circulatory conditions are more favorable in that the chief (and with closed foramen ovale, the only) cause of raised oxygen-unsaturation is retardation of flow with increased deoxygenation in the capillaries. . . . Cyanosis is therefore usually moderate in degree and of relatively late onset, frequently not appearing until after early childhood. The condition tends, too, to become progressive. . . . There may be an enlarged pulmonary arc from dilatation of the pulmonary trunk above the valve; and right predominance is a marked feature of the electrocardiogram.

The clinical diagnosis in this case was congenital pulmonary stenosis, probably associated with some other anomaly. As Abbott noted, uncomplicated pulmonary stenosis is less common than "the developmental type of pulmonary stenosis associated with ventricular defect and dextroposition of the aorta." This complex ("tetralogy of Fallot" or "biventricular aorta with pulmonary stenosis" [9]) is the most common cause of deep lifelong cyanosis in an adult. It could not of course explain the case of C. S., because the cyanosis and clubbing were both mild, the ascending aorta was not dilated, and the pulmonary trunk was dilated.

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9. Blackford, L. M.; Davenport, T. F., and Bayley, R. H.: Right Aortic Arch: I. Clinical Report of a Case with Associated Anomalies, Am. J. Dis. Child. **44**:823-844 (Oct.) 1932.

Blackford and McGehee [10] noted in 1933 that in the majority of cases of congenital heart block the clinical diagnosis is patent interventricular septum. At the time of that report a review of the literature showed that "this defect was present in the 5 patients that came to necropsy. The atrioventricular bundle studied microscopically in 3 was imperfectly developed." It seemed reasonable then to conclude that in cases of congenital heart disease interference with the conduction system was a result of imperfect development and that this was associated with a defective interventricular septum. Therefore, in the case of C. S. the interference with conduction was interpreted as evidence in favor of a defect in the muscular part of the interventricular septum.

The illness in infancy raises a possible doubt. It is not improbable that C. S. never had a physical examination prior to that illness, and his mother may have exaggerated the importance of the ailment. It is quite possible too that she experienced an acute infection a few months before the child was born and twenty-four years later had forgotten it. The valvular lesion appeared to be the late result of an inflammatory process; one thing we can be sure of is that this infection occurred after the fundamental structures of the heart had been completed. However Lewis [11] described congenital pulmonary stenosis as follows: "Pulmonary stenosis of simple form is a very rare condition in which a strong membranous partition perforated centrally by a small circular aperture is found at the origin of the pulmonary artery." It is our present opinion that this infection was prenatal.

Since the left ventricle did not come in contact with the anterior wall of the chest, a bifid apical thrust could not be seen or felt. The sound tracings indicated that the first sound was not audible at the apex, but they did not show reduplication, gallop or asynchronous murmurs. Bundle branch block, in our opinion, could not have been diagnosed in this case without the electrocardiogram.

The histologic studies indicated that the changes in the myocardium were the result not of chronic inflammation but of ischemia. This ischemia seemed to have been caused by mechanical factors involved in the distortion of the interventricular septum secondary to the tremendous hypertrophy of the right ventricle required to overcome the resistance of the 6 mm. pulmonary orifice. At the same time it must be admitted that the thickening of the arterial walls may have interfered to some extent with the blood supply. The histologic studies of the conduction system did not include the two branches. Such studies seemed unneces-

10. Blackford, L. M., and McGehee, H. M.: Congenital Heart-Block: A Case with Other Cardiac Anomalies in a Student of Twenty-Three Years, Am. Heart J. **9**:96 (Oct.) 1933.

11. Lewis, T.: Diseases of the Heart, ed. 2, New York, The Macmillan Company, 1937, p. 266.

sary, for Yater's work is generally accepted as conclusive. In short, our studies support the opinion of Yater and of Bischoff, as well as of earlier writers, that bundle branch block is usually due to interference with the blood supply to the septum.

The histologic examination of the myocardium emphasized a point of clinical importance. Paroxysms of tachycardia occur frequently in persons with normal cardiovascular systems and in such persons, once the diagnosis is made, are rarely worthy of any concern. One is therefore apt to forget that attacks of rapid heart action are more common in diseased hearts than in normal hearts and that when they speed up a seriously damaged heart, the outlook is grave, as was emphasized recently.[12] In this case it seems quite possible that the paroxysms of tachycardia were ventricular in origin, and that the patient died in such a paroxysm. In retrospect, therefore, his death might have been expected at any time during several months.

The depression that C. S. experienced after graduation has been noted. The disappointments he experienced seemed at the time to offer adequate explanation, but one may wonder now if his depression was not more the result of an ill defined sense of impending death.

SUMMARY

A case is presented of pulmonary stenosis with right bundle branch block occurring in a man who died at 23. Congenital pulmonary stenosis was diagnosed several years before his death, but the electrocardiogram was interpreted as evidence of a septal defect.

Sound tracings lent little support to the opinion that bundle branch block can be diagnosed with the stethoscope.

Histologic studies confirm the thesis that the cause of bundle branch block is often interference with the blood supply of the interventricular septum.

Paroxysms of tachycardia in cases of serious heart disease indicate a grave prognosis.

12. Blackford, L. M.: Mitral Stenosis as a Cause of Angina Pectoris, Am. Heart J. **20**:492-497 (Oct.) 1940.

SYNDROME OF DESTRUCTION OF THE PINEAL GLAND

EXPERIMENTAL AND CLINICAL OBSERVATIONS

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Among those organs of the body the physiology of which still remains incompletely understood, no one structure has caused more diversity of opinion or argumentative disagreement than has the pineal gland. It has been studied anatomically in almost every branch of all the vertebrates; since the turn of the present century all manner of physiologic experiments have been performed in the attempt to prove or disprove its endocrinal potentialities, and, recently, pineal substance and so-called pineal extracts have been used hopefully in opotherapy. Overenthusiasm to disclaim or substantiate a physiologic function for the pineal gland, on the one hand, has been balanced by the attitude of neglect, confusion or evasion, on the other, the net result being a voluminous, rambling, bewildering and unconvincing literature.

The preponderant anatomic evidence at hand indicates the glandular possibilities of the pineal gland in the early stages of life in most vertebrates, though this will not be conceded to be true by all neuroanatomists.[1] Extensive and carefully performed phylogenetic investigations do not support the theory that the pineal gland in mammals is a remnant of the reptilian midline eye.[2] Anatomic facts alone are insufficient for a complete understanding of the physiologic significance of the pineal gland; more recent studies have been concerned with the physiologic action of pineal products in immature animals, the relation of such secretions to the known glands of internal secretion and the part played,

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From the Division of Surgery, Northwestern University Medical School, and the Cushing Tumor Registry, Yale School of Medicine.

1. Río-Hortega, P.: The Pineal Gland, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2.

2. Tilney, F., and Warren, L. F.: A Contribution to the Study of the Epiphysis Cerebri with an Interpretation of the Morphological, Physiological, and Clinical Evidence, American Anatomical Memoirs, Philadelphia, Wistar Institute of Anatomy and Biology, 1919, no. 9. Tilney, F.: The Pineal Gland, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, 1928, vol. 1, p. 503.

if any, in the maturation of the individual animal. Extirpation or implantation of the gland and the administration of pineal substance have been the paths of approach used by physiologists. That the results of these studies have varied widely, conflicted and given no final solution hardly needs to be emphasized here. Tumors of the pineal gland alone in human subjects, or in conjunction with pathologic processes in the adrenals, gonads or hypothalamus (including the pituitary), have led clinicians into a state of doubt and indifference.

The time of the preparation of the present report (July 1940) marks the end of a four and a half year period during which the experimental phase of our investigations has had to do with the extirpation of the pineal gland in rats, cats, dogs and monkeys. Implantation of the pineal gland or the administration of pineal substance or extract has not yet been carried out, for it was our primary aim to observe in a conclusively large enough series of animals the effects of destruction of the pineal gland alone (apinealism) early in life, when there is actual histologic evidence of glandular function. All pinealectomized animals were controlled by litter mates of the same sex; both lesion and control animals were reared under equal and standard laboratory conditions, and a complete life history was recorded for each animal. We have been concerned with the growth and maturation, both somatic and sexual, in animals of both sexes from which the pineal gland was removed at an early age. We have tried to evaluate those changes in behavior which have been unquestionably present, and we have compared the reproductive cycles of the pinealectomized animals with those of their normal litter mates.[3] In addition, we have compared the histologic characteristics of many of the organs of the pinealectomized animals with those of their controls, and animals which have been castrated or hypophysectomized or both are now being reared in the laboratory to show what the effect of such treatment may be on the histologic development of the pineal gland at various ages. A minor portion of our histologic observations has already been reported,[3] and the completed report will be forthcoming at a suitable time.

This communication has to do with certain of our data obtained on animals, which we believe should be presented in conjunction with the results of an analysis of a large series of tumors of the pineal gland in human beings.

Cats have been used extensively in our investigations because, for several reasons, they are well adapted to such use. The cat skull offers no surgical difficulties; the cat has a well developed mammalian brain, with definite and easily recognized landmarks; the cat is well up in

3. Davis, L., and Martin, J.: Results of Experimental Removal of Pineal Gland in Young Mammals, Arch. Neurol. & Psychiat. **43**:23-45 (Jan.) 1940.

the phylogenetic scale, and litters are usually of such size as to allow at least 2 lesion animals and 1 control of one sex in each litter. Furthermore, the cat is an inexpensive animal to maintain, and it is well adapted to laboratory life. Because of the facility with which accurate lesions may be made in the cat brain with the aid of the Horsley-Clarke stereotaxic instrument, the cat seemed especially useful, and the great majority of our animals have been pinealectomized by this means.

At the present time 108 cats have been studied, of which 68 were males and 40 were females. All except 6 were successfully pinealectomized with the Horsley-Clarke instrument. Four cats were pinealectomized by means of retracting the cerebral hemisphere, splitting the splenium of the corpus callosum and plucking out the gland, but all of these animals died within a few days of their operation. The average age of the kittens at operation was 6½ weeks, and autopsy studies have been completed on cats killed at periods varying from immediately after operation to thirty-five months later.

At the time of operation the kittens were numbered, classified as to sex, weighed, measured from crown to rump, given a roentgen examination and photographed; several were given an injection of 1 cc. of 2 per cent aqueous solution of alizarin red to indicate the rapidity of bone growth, since the dye is deposited by the periosteum in ring formation in the cortex of growing bones. With the kittens under anesthesia induced by phenobarbital sodium, the scalp was shaved, cleansed and surgically opened over the vertex. After careful placement of the Horsley-Clarke instrument, a small burr hole was made in the skull over the midline, and, according to predetermined coordinates, a small electrode, insulated except at the tip, was passed through the sagittal sinus, along the falx, through the splenium of the corpus callosum and into the pineal gland. Adequate galvanic current was then used to coagulate and destroy this structure. The skin was closed with clips, and the animals were allowed to recover in a warm box. They were able to eat and drink within twenty-four hours, and there was no instance of infection of the wound following the operation. Weekly weights and measurements were recorded; behavior characteristics showing any variation from the normal were observed; all illnesses and feeding difficulties were noted, and roentgenograms, photographs and injections of alizarin were repeated at definite intervals.

There were no significant differences in the somatic development of the control and the pinealectomized female cats, but when the entire series were reviewed and the time of the first estrus noted, it was found that the normal female cats experienced estrus at an earlier date than did their pinealectomized mates. Control females mated with pinealectomized males produced small litters of no more than 4 kittens, which were usually feeble, often dying of starvation after twenty-four to forty-eight

hours because of their inability to nurse. The pinealectomized mothers likewise had small litters, which they tended to drop three or four days before term, with the kittens dead or, if alive, frequently too feeble at birth to nurse properly. Only 3 pinealectomized mothers had an adequate supply of milk, the others showing slight or no breast changes at parturition and responding only moderately to injections of prolactin. In most instances the pinealectomized mothers showed but little maternal instinct, frequently ignoring their kittens for hours, covering them with straw and making few attempts to encourage the kittens to nurse. Two such mothers failed to dispose of the placentas and to disengage the newborn litter from the entangled cords and membranes. We have

TABLE 1.—*Average Weights and Lengths (Crown-Rump) at Various Critical Periods*

	Control	Lesion Animal
A. Male cats		
At operation, approximately 6½ weeks of age		
Weight	838 Gm.	830 Gm.
Length	26.0 cm.	25.6 cm.
Nine months of age		
Weight	2,226 Gm.	3,118 Gm.
Length	40.1 cm.	45.5 cm.
Complete adult status, approximately 15 months of age		
Weight	2,900 Gm.	3,656 Gm.
Length	42.5 cm.	46.4 cm.
B. Female cats		
At operation, approximately 6½ weeks of age		
Weight	709 Gm.	727 Gm.
Length	26.7 cm.	25.6 cm.
Nine months of age		
Weight	2,381 Gm.	2,490 Gm.
Length	41.1 cm.	41.3 cm.
Date of first estrus (see table 2)		
Weight	2,650 Gm.	2,701 Gm.
Length	42.6 cm.	42.4 cm.

found it much more difficult to rear the kittens of pinealectomized cats than those of normal cats.

The average normal male cat shows no sexual interest before 13 or 14 months of age, and until 8 or 9 months of age our male cats all showed much the same behavior. But at the age of approximately 9 months the pinealectomized male cats began to be less playful, exhibited sexual interest in female cats, were heavier and had a larger skeleton than did their controls. They had larger external genitalia than did their controls, had frequent erections and were sexually potent. Growth continued in both the control and the lesion animals until the age of 15 or 16 months, but when growth had ceased and all the animals were mature, the lesion animals were in every instance larger. All significant organs were removed at autopsy, weighed fresh and studied histologically.

Tables 1 and 2 indicate the growth and sexual development of the cats used in this study and make evident the following facts: 1. At the

age of 9 months the pinealectomized male cats were sexually mature and were longer and heavier than their normal controls. 2. When complete body growth was attained in both lesion and control animals, the lesion animals were notably the larger. 3. There were no important differences in the somatic development of the female cats. 4. The pinealectomized female cats experienced their first estrus at a later date than did their normal controls.

Second generation cats, the offspring of certain of the cats with which the foregoing data are concerned, have been reared with innumerable difficulties and with a high mortality in the early weeks of life. Thirty-seven male and 16 female second generation cats have been born. As previously noted, they were in most cases weak and undersized at birth, grew slowly and got off to a slow start in early life.

TABLE 2.—*Data Indicative of Sexual Maturity*

Average breeding age	
Male controls	14.0 mo.
Male lesion cats	9.6 mo.
Average age at which first estrus appeared	
Female controls	11.9 mo.
Female lesion cats	14.8 mo.

TABLE 3.—*Data on Second Generation Cats*

	Male	Female
Born dead	4	1
Lived 1 week	9	3
Lived 8 to 35 days	8	4
Lived 1 to 3½ months	8	8
Now living, various ages up to 1 year	8	0

They contracted infections of the eyes and sinuses in spite of constant vigilance and special care. They were reared side by side with kittens born to mothers brought pregnant into the laboratory, and the litters of the latter have thrived, while those of the pinealectomized parents did not. Table 3 furnishes some indication of the rate of their early mortality.

Eight male and 2 female cats of the second generation have been operated on, all with litter mate controls. Now living are 2 male controls, 4 male pinealectomized kittens and 2 cats which were controls of lesion litter mates which died early. This, of course, is too small a series to offer any conclusive data, but it may be stated that the pinealectomized males are already showing gains in weight and length over their controls, similar to those seen in the early months of development of their ancestors.

Two male dogs (litter mates) and 2 female dogs (litter mates, but not related to the males) and 3 second generation pups are now under observation. The lesion animals were pinealectomized by manual removal

of the gland through a small craniectomy after the splenium of the corpus callosum had been incised. The male dogs were operated on at 5 weeks of age; the females, at 6 weeks. Complete life histories of these animals have been kept, with records of weight, skeletal growth, sexual development and behavior characteristics. Table 4 indicates the manner in which the pinealectomized male dog outstripped his control in both growth and sexual development and the little developmental difference in the 2 female animals. However, at 17.5 months of age the normal female dog experienced her first estrus, mated and after a normal period of gestation littered 1 female and 2 male pups. The pinealectomized female dog has not yet shown any signs of estrus (at 20 months of age) a delay in development similar to the late appearance of estrus in the pinealectomized female cats.

The results of our investigations on rats have been reported elsewhere.[3] Briefly stated, those results showed an increased somatic development in the male animals, no particular difference in growth in the female animals and the histologic evidence of puberty in all animals at the age of autopsy, 90 days. Three male and 2 female Macacus rhesus monkeys are now being studied in the laboratory.

In the files of the Cushing Tumor Registry, at the Yale School of Medicine in New Haven, Conn., there are the histories of 18 patients whose cases are classified under "tumors of the pineal gland." Every case was verified by operation or autopsy or both; the clinical records are complete in detail, and in every instance complete and careful histologic reports of the surgical and autopsy specimens are available. For these reasons an analysis of the symptoms of these 18 patients should furnish reliable information concerning the pineal syndrome in man.

Such a detailed analysis has recently been made, and in this review not only were surprising facts revealed concerning changes in somatic and sexual maturation, but it was apparent that collectively the patients presented a pattern of symptoms that occurred in a more or less constant chronologic order and that, when summarized, appeared to constitute a "typical" pineal syndrone, which might conveniently be illustrated by a hypothetic case history. Such a hypothetic case could be substituted with no sacrifice of accuracy for any one of several of the histories in the verified series. It was found that three periods are usually distinguishable in the history of the patient with a tumor of the pineal body. Headache is consistently the first symptom to appear, and it antedates the other, more localizing, symptoms by several weeks, during which time there is a general decline in the patient's condition. The second period is usually ushered in by blurring of vision, diplopia, change in mental outlook, ataxia, increasing drowsiness, permanent changes in the pupils, transient convulsions, disturbances of the heat and water meta-

bolism-regulating centers and, finally, permanent paralysis of the various extraocular muscles, especially those having to do with conjugate upward gaze. In the final stage, during which the patient may first come under careful observation, papilledema or optic atrophy, marked weakness, varying degrees of spasticity, a low temperature and a low basal metabolic rate appear. Air injection studies reveal the typical displacement of the ventricles and advanced internal hydrocephalus, associated with destruction of the walls of the third ventricle.

The symptoms of somatic and sexual precocity must be considered separately, for tumors of the pineal gland may, of course, appear so late in life that precocity is not a point for consideration. In the Cushing

TABLE 4.—*Weights and Lengths (Crown-Rump) at Various Critical Periods*

	Age	Category	Weight, Lb.	Length, In.
A. Male dogs	5 wk.	Control	3.5	9.9
		Lesion	3.5	10.2
	3 mo.	Control	6.8	16.1
		Lesion	11.0	19.5
	8 mo.	Control	20.5	23.5
		Lesion	29.0	26.3
		Lesion dog sexually mature at 8 months of age		
	11 mo.	Control dog sexually mature at 11 months of age		
	20 mo.	Control	23.0	24.5
		Lesion	34.0	27.5
B. Female dogs	6 wk.	Control	4.5	12.6
		Lesion	5.3	13.0
	3 mo.	Control	9.0	17.25
		Lesion	10.0	18.0
	8.5 mo.	Control	14.75	21.75
		Lesion	16.75	22.0
	17.5 mo.	First estrus of control, followed by normal pregnancy and delivery of 3 pups		
	20 mo.	Control	16.75	22
		Lesion	16.75	23
		No evidence of estrus in pinealectomized female		

series there are 11 pinealomas, 4 pineoblastomas, 1 teratoma and 2 ganglioneuromas, 1 of which also showed multilocular cystic degeneration of the pineal body. Fourteen patients were males and 4 were females. Four boys, aged 3, 7, 9 and 12 years, presented cases of pubertas praecox in a moderate to a marked degree, and this is borne out not only by the somatic and sexual maturation in advance of their chronologic age, but also by microscopic study of the testes in those cases in which a complete autopsy was done. According to Dr. Cushing's note, there was "multilocular cystic degeneration of the pineal gland" coupled with a "massive firm tumor of the third ventricle" (a ganglioneuroma) in the 7 year old boy, whose symptoms of precocity, incidentally, were quite evident at birth, but in the other 3 boys of this group there was a primary tumor of the pineal gland.

Sexual precocity was suspected in a lad of 6 years, and another patient, aged 17 years, was said to have shown unusually strong libido on attaining puberty, at the age of 14 years. Somatic precocity was evident in the 4 boys aged 3, 6, 7 and 12 years, since their musculature and body form were in advance of that usual for their age. Mental precocity was a prominent symptom in 2 of these boys who were both physically and sexually precocious. Of the 14 male patients, then, ranging from 3 to 40 years of age, all 5 of those 12 years of age or under showed definite evidence of somatic or sexual precocity or both.

Two adolescents, aged 13 and 20 years, suffered from sexual dystrophy and regressions of sexual characteristics once well developed, but there were no somatic changes other than the usual emaciation. These patients were first seen in the advanced stage of their disease, and autopsy revealed in 1 case that tumor was seeded into the walls of the third ventricle and infundibulum and in the other that solid tumor tissue extended from the pineal gland into the anterior portion of the third ventricle.

Three adult male patients were married, but none had any children. All were considered to be sexually potent, but 1 man had been married only three and a half months. Apparently, in these 3 patients the onset of the disease was well after the attainment of puberty.

The 4 female patients were aged 10, 13, 15 and 29 years. Amenorrhea was present in all 4 patients, but the 29 year old woman had been married two years and had a 6 month old, normal child. A female patient, aged 19 years, in our own series likewise suffered from amenorrhea. There was no evidence of somatic or sexual precocity in any of these female patients, and the amenorrhea was the only evidence of sexual dystrophy in the subjects older than the 10 year old, prepuberal girl.

In addition to these facts concerning body growth and sexual maturation, other interesting data came to light in this analysis. Polydipsia or polyuria alone or together was present in 8 patients, and 1 patient, a girl of 15, suffered polyphagia, especially for sweets. Six patients consistently had subnormal temperatures; 10 patients showed loss in weight and generalized cachexia, while the 2 girls aged 13 and 15 showed some gain in weight during the last seven months of life. Terminal apathy and somnolence were marked in all but 4 patients; pigmentation of the skin occurred in 4 patients; 6 patients were definitely hypotensive, and the 4 patients for whom basal metabolic readings had been recorded showed values ranging from — 24 to — 38 per cent. These more critical laboratory data were obtained during the late stages of the disease, when apparently hypothalamic-hypophysial dysfunction had resulted from advanced invasion by the tumor or from pressure destruction of those structures.

It is generally conceded that disease of the diencephalon produces changes the results of which may cloud, rather than elucidate, the function of that part of the brain, and there is certain to be a great overlapping of symptoms in the presence of an old or a large tumor of the pineal gland which causes destruction of the vegetative centers of the diencephalon. Certainly, in many of the 18 cases of tumor studied there were unmistakable pathologic changes extending beyond the pineal gland itself. The pituitary body, the walls and floor of the third ventricle and the periaqueductal gray matter are, of necessity, injured by a large or "seeded" tumor of the pineal body. Obviously, the solution of the function of the pineal gland does not lie in an analysis of the symptoms found in patients who have suffered from destruction of other areas which are as important as the pineal gland. This solution must come from the recognition of the changes which follow destruction of the pineal body alone, without the occurrence of additional damage to the brain. Teratoma of the pineal gland is primary and present at an early age, and it is, in the majority of cases, accompanied by signs of precocious development. But that teratoma is the sole cause of precocity, as has at times been reported, is certainly not supported by the evidence from the tumors in the Cushing series. It is impossible to say whether all 5 of the male patients with evidence of premature development, and seen for the first time when their disease was well advanced, had signs of such precocity when the tumor of the pineal body was small, local and without hypothalamic or hypophysial effects of a mechanical nature, though it does appear from the case histories that such signs of early maturation were the first to appear in those patients whose early history was recorded. It is worth noting that developmental changes are not particularly common when obstruction and pressure destruction are caused by a lesion, for example in the posterior fossa, in the absence of pathologic changes in the pineal body; it would seem that destruction of the diencephalon by pressure from obstructive hydrocephalus alone is not sufficient to cause such changes in maturation, regardless of the source of the obstruction. Large tumors of the pituitary gland, craniopharyngioma, cyst of the third ventricle, basilar meningioma and other tumors which cause local destruction of the walls and floor of the third ventricle certainly do not commonly produce somatic and sexual precocity in the young patient.

None of our animals in which there was destruction of the pineal gland at an early age showed any polydipsia, emaciation, polyuria, obesity, somnolence, hypothermia, stupidity or infantilism, such as was seen in the patients who had not only a tumor of the pineal body but also widespread destruction of the walls and floor of the third ventricle. As in the patients, early somatic and sexual development were noted only in the male animals, with a corresponding maturity of behavior.

None of these animals at autopsy showed any evidence of hydrocephalus, atresia of the aqueduct of Sylvius or destruction of the hypothalamus. In keeping with the less prominent somatic changes in the female patients, our female pinealectomized animals showed no premature body growth. Amenorrhea in the female patients may be compared with the delayed appearance of the first estrus in our pinealectomized female animals and their subsequent variations from the normal reproductive activity.

Thus, it appears to us not too optimistic to compare the results of apinealism in a large series of experimental animals and the corresponding pertinent data relative to sexual and somatic maturation in a large series of cases of tumor of the pineal body in human subjects. No claim is made that the two sets of data tally, fact for fact, for, on the one hand, there was simple, primary destruction of the pineal gland in a laboratory animal, while, on the other, the destruction in man was attended by secondary changes which prevent the attempt to read into the symptoms the answer to the question of the function of the pineal gland. There can be no question concerning the implications of the findings in both the laboratory and the clinical subjects, however, and it is especially indicated that the syndrome of destruction of the pineal gland alone and the effects of resultant endocrine-like changes will most likely be found in the experimental laboratory, to be supported and corroborated by carefully managed clinical investigations.

VITAL CAPACITY OF THE LUNGS IN MIDDLE AGE

RESULTS OF PERIODIC EXAMINATIONS OF MEN OF SEDENTARY OCCUPATION

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The vital capacity of the lungs is the amount of air which can be exhaled after the deepest possible inspiration.[1] Obviously, any disease which encroaches on the parenchyma of the lungs (pneumonia, congestive heart failure, etc.) or which interferes with the normal movements of the bones or muscles involved in respiration (immobility of the ribs, paralysis of the phrenic nerve, etc.) or which prevents the free movement of air in the respiratory passages (bronchogenic carcinoma, asthma, etc.) will diminish the vital capacty. That these conditions, as well as numerous others, actually do diminish the vital capacity has long been recognized, and the test of vital capacity would no doubt be a widely used diagnostic office procedure today if the patient could only tell the examiner as much about his vital capacity as he can about his weight. Most patients know what they weighed a year ago and how their weight varies from season to season. Such is not the case with the vital capacity. Seldom does one encounter the patient who can tell the examiner what he "blew" last year, and never one who can give information regarding variations in his vital capacity. Attempts to overcome this handicap have resulted in the construction of formulas for predicting the vital capacity from the height, weight, age and other factors known to influence the vital capacity. Such formulas have their value, just as weight tables have, but are subject to grave limitations. One person may be 15 per cent below the standard and yet be in perfect health, while another may be above the standard and yet have pulmonary tuberculosis. For this reason the test has largely been discarded as a diagnostic procedure.

In certain groups, however, it is possible to secure periodic readings of vital capacity in health to serve as a basis for comparison with readings secured during any illness which might later occur. I have used the test of vital capacity in this manner with satisfaction in the Student Health Service of Drexel Institute of Technology for the past ten years.

1. Hutchinson, J.: Med.-Chir. Tr., London **29**:137, 1846.

To subject the impressions of this procedure to statistical scrutiny, the records of 100 male and 100 female college students over a period of three or four years were analyzed by Arnett and De Orsay.[2] Each student's tendency to gain or lose could be represented by his "best straight line," sloping upward or downward as the case might be. The magnitude of individual variations from such a line would then have to to be taken into account in interpreting any readings observed during illness. It was found that the variations were not large enough to interfere with the usefulness of the test in the diagnosis of diseases accompanied by a pronounced fall in the vital capacity—pneumonia, for example—but that about one third of the students exhibited standard deviations of sufficient magnitude to render the test of questionable value in the diagnosis of conditions in which slight losses in vital capacity were to be expected—early tuberculosis, for example.

METHOD

The need for a similar study on persons of middle age becomes obvious, since it has never been determined whether the vital capacity is less variable or more so at this time of life. The present study was, therefore, made on men of sedentary occupation who presented themselves annually for a health examination. The latter included a complete history, physical examination, urinalysis, blood count and electrocardiogram. Roentgenograms of the chest were made when indicated. The group, therefore, constituted an ideal one for the purpose of this study. I made determinations of the vital capacity at the time of each annual examination, using the same spirometer throughout; the usual technic employed entailed at least three trials for each determination. Persons exhibiting a fall in vital capacity attributable to demonstrable causes, such as myocardial or pulmonary disease, have been omitted from consideration. The mean age at the time of the first examination was 48.7 years, the oldest man being 66 and the youngest 31.

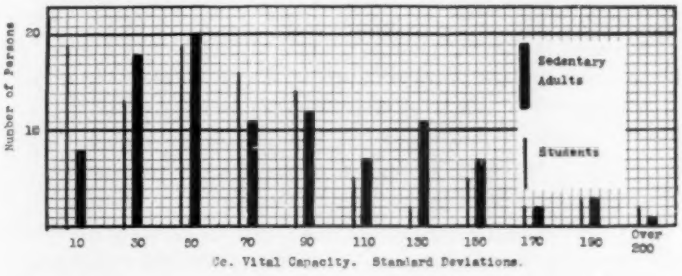
RESULTS

The results indicate that the vital capacity is not as useful a diagnostic procedure for the present group as for the students. The chart shows clearly the greater deviations in vital capacity in the present group, and when analyzed statistically, the difference is found to be significant. Interpreting it from the standpoint of usefulness in diagnosis, one could broadly state that in no case were the deviations from the "best straight line" of sufficient magnitude to interfere with the usefulness of the test in diagnosing pneumonia, but that for diseases exhibiting slight dimi-

2. Arnett, J. H., and De Orsay, R. H.: Am. J. M. Sc. **193**:684 (May) 1937.

nutions of vital capacity the test could be applied with confidence only to about half of the group. For example, if three times the standard deviation is taken as the criterion of significance and 250 cc. as roughly representing the loss in vital capacity to be expected in early tuberculosis, determination of the vital capacity would be a reliable test for 54 of the present group, as compared with 68 of the young men of the previous study.

Further comparison of the present group with the younger men reveals that 63 of the older men exhibited losses in vital capacity, 11 remained the same and 26 gained, the average man losing 33.7 cc. per year,[3] the greatest annual loss being 250 cc. and the greatest annual gain being 200 cc. Among the students only 12 lost, 72 gained and 16 remained the same, the average student gaining 66.9 cc. per year, the greatest annual gain being 400 cc. and the greatest loss 90 cc. These



Deviations in vital capacity from year to year. Deviations are expressed in terms of the standard deviation from the "best straight line" which could be drawn through the points representing all of the determinations of vital capacity.

figures are not surprising. Hutchinson, computing the average of single readings made on persons of different ages, concluded that after the age of 30 the vital capacity tends to diminish at the rate of 1.43 cubic inches (23.5 cc.) per year.

CONCLUSIONS

The test of the vital capacity of the lungs is a useful diagnostic procedure, provided its potentialities and limitations are understood.

Its greatest field of usefulness is in groups subjected to periodic examinations.

The present study indicates that the test is more valuable for men of college age than for middle-aged men of sedentary occupation.

3. The figures given represent the slopes of the best straight lines, these being derived from the regression formula $Y = a + b(x - \bar{x})$; see Fisher (Statistical Methods for Research Workers, ed. 3, London, Oliver & Boyd, Ltd., 1930, pp. 114-115).

EFFECT OF UREMIC SERUM AND URINE ON GROWTH OF FIBROBLASTS IN VITRO

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Since the introduction of chemical analysis of blood in the investigation of renal disease and the use of tests of renal function, true uremia is considered as poisoning due to retention in the blood of urinary waste products. Almost every urinary constituent has been considered as the basic substance which causes the clinical symptoms displayed by patients with uremia. The attempt, however, to hold a single "uremia toxin" responsible for the clinical picture of uremia has failed. No single substance has been discovered the retention of which, as a result of renal insufficiency, produces uremia. The concept prevailing now (Volhard,[1] Fishberg[2] and Harrison and Mason[3]) has been clearly expressed by Fishberg: "Uremia is a complex autointoxication, the variegated clinical picture being the summation of the effects of retention of various urinary constituents." The most important substances which are considered as playing a role in the production of the uremic syndrome are the phenols, guanidine and urea. The mechanism of some of the clinical manifestations of uremia is ascribed also to disturbances of mineral metabolism. However, the possibility is not excluded that some, or possibly many, undefined substances are also concerned in the pathogenesis of uremia (Harrison and Mason[3]).

In view of the fact that the chemical analysis of body fluids and the investigation of the pharmacologic action of retained metabolites have not fully clarified the problem of uremia, old experiments concerning the toxicity of uremic blood and urine are still of interest, The methods

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1. Volhard, F., in von Bergmann, G., and Staehelin: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1931, vol. 6, pt. 1, p. 776.

2. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930.

3. Harrison, T. R., and Mason, M. F.: The Pathogenesis of the Uremic Syndrome, Medicine **16**:1, 1937.

used in the latter experiments consisted of injecting uremic blood or urine into animals and observing the effect, The first to carry out experiments of this kind was the French clinician Bouchard,[4] in 1887. He found that normal human urine had a toxic effect on animals. Forty-five cubic centimeters of urine injected into the vein of a rabbit produced a lethal result. On the other hand, the urine of uremic patients was less toxic than that of normal persons.

The lesser toxicity of uremic urine was considered by Bouchard as evidence of retention in the blood of urinary toxins in uremia. Supplementary to these experiments were the subsequent ones of Roger [5] and Herter.[6] Roger injected blood serum of uremic patients into dogs and caused toxic manifestations similar to those of uremia. Herter made the same observations with blood serum obtained from dogs the ureters of which were ligated on both sides.

Serious objections were made to the method of demonstrating the toxicity of uremic serum and urine on experimental animals. The view has been expressed by investigators repeating these experiments (van den Bergh,[7] Albu [8] and Volhard [1]) that the rate of injection was of greater significance for the result of the experiment than was the quantity of the injected serum or urine. The effect of foreign serum proteins might also lead to misinterpretation of the toxicity of uremic serum. In the experiments with urine injected into animals, great importance was assigned to the concentration of the urine and to the effect produced by the hypertonicity of the urine, which effect was wrongly interpreted by Bouchard and his pupils as being due to specific toxic properties of urine. Finally, the varying individual sensitivity of the experimental animal to the injected urine or blood was considered as one of the disadvantages of this method.

It seemed therefore justified to reinvestigate the problem of toxicity of uremic serum and urine by new methods. Tissue culture appeared to offer a suitable method for testing the general toxic nature of the materials concerned. Cell colonies growing in vitro form a convenient test object showing fundamental vital phenomena. The ingredients of the mediums which determine the growth of the cell colonies can

4. Bouchard, C.: Leçons sur les autointoxications dans les maladies, Paris, F. Savy, 1887.

5. Roger, cited by Fishberg.[2]

6. Herter, C. A.: The Results of Experimental Nephrectomy in Dogs as Bearing upon the Uraemic State, M. Rec. **52**:280, 1897.

7. van den Bergh, A. A. H.: Ueber die Giftigkeit des Harns, Ztschr. f. klin. Med. **35**:53, 1898.

8. Albu, A.: Experimentelle Beiträge zur Lehre vom Harngift, Virchows Arch. f. path. Anat. **166**:77, 1901.

be changed as required, and blood serums and urines to be examined can be added. The growth in the altered milieu can be measured and compared with control cultures, and the cell-toxic properties of the blood serums and urines to be examined can be deduced from the degree and nature of the effect of these substances on the development of the cell colonies.

EXPERIMENTAL METHODS

Uremic serum and urine were taken from patients suffering from severe renal insufficiency. In all cases, urea and uric acid were retained in the blood in varying degree and the usual clinical symptoms of uremia were present. Cases of uremia with complications, such as fever or icterus, were omitted from these series of experiments.

The pathologic serums and urines were tested on cultures of fibroblasts originating from chick embryo hearts. After three passages in hanging drops, the cultures were transferred to flasks and cultivated according to Carrel's standard method. The solid phase of the medium consisted of chick plasma diluted with Tyrode's solution, in the proportion 1:2, coagulated by 1 drop of diluted embryonic extract. To this was added as liquid phase the blood serum or sterile urine under examination. In experiments with uremic serum, the control flasks contained the same quantity of normal serum. In experiments with uremic urine, the control flasks contained the same quantity of Tyrode's solution or, in some cases, of normal urine.

In some of the experiments the effect of pathologic serums on cultures stimulated with embryonic extract was examined, the liquid phase in the test flasks consisting of embryonic extract and uremic serum, while to the control flasks embryonic extract and normal serum were added.

All experiments were carried out on sister cultures, one being used for the test experiment and the other for the control. The growth of the cultures was examined for a period of five to eight days, without change of the medium. The cultures were projected every day and were drawn and measured with a planimeter in accordance with Ebeling's method. The resulting values were used in plotting the growth curves.

INFLUENCE OF UREMIC SERUM ON GROWTH OF FIBROBLASTS IN VITRO

Behavior of Fibroblast Cultures in a Medium Containing Normal Human Serum.—In a series of preliminary experiments the influence of normal human serum on the growth of chick fibroblasts in vitro was examined. Comparison was made between the growth of fibroblasts in flasks to which serum of healthy persons was added as liquid phase and that of fibroblasts in flasks to which Tyrode's solution was added. The experiments showed that the fibroblasts in mediums containing normal human serum developed regularly; during the period of observation of seven to eight days the increase in area of the cultures was constant (fig. 1). The dimensions reached by the cultures at the end of this period ranged between 10 and 12 mm.^{2} These values corresponded to those reached by the cultures in the flasks with Tyrode's solution as liquid phase. Thus, the experiments showed neither a stimulating nor an inhibitory influence of the serum on the proliferation of cells. The appearance of the cultures in the flasks with serum

differed, however, from that of cultures growing in Tyrode's solution. The zone of growth of the latter appeared to be flat and the cultures were always transparent, while the serum cultures were more dense and compact, particularly in the central regions.

Behavior of Fibroblast Cultures in a Medium with Uremic Serum.—EXPERIMENT 1: A 37 year old patient (Miz.) was suffering from acute uremia, which appeared after a blood transfusion. At the time of the first observation, the urea content of the blood was 381 mg. per hundred cubic centimeters.

The effect of the serum on cultures stimulated with embryonic extract was investigated. The liquid phase of the test flasks consisted of 0.5 cc. of the patient's

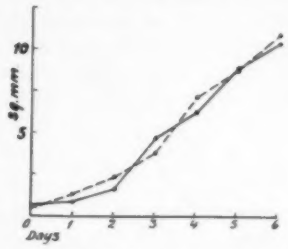

Fig. 1.—Growth curves of fibroblasts in normal serum (solid line) and in Tyrode's solution (broken line).

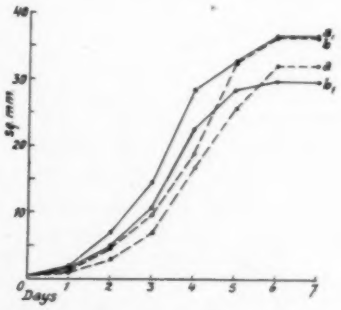

Fig. 2 (patient Miz.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by a and a_1 and b and b_1.

serum and 0.5 cc. of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration, with the same quantity of normal human serum. The growth curves of both pairs of cultures are shown in figure 2.

A few days later, the urea content of the blood of the same patient was 414 mg. per hundred cubic centimeters, and the experiment just described was repeated under identical conditions. The results are shown in figure 3.

Results: The addition of uremic serum with a high urea content (381 and 414 mg. per hundred cubic centimeters) had no injurious effect on the growth of the fibroblasts. The rate of growth was either the same or, as in the second part of the experiment, even slightly greater than normal. The appearance of the proliferating cells was entirely normal.

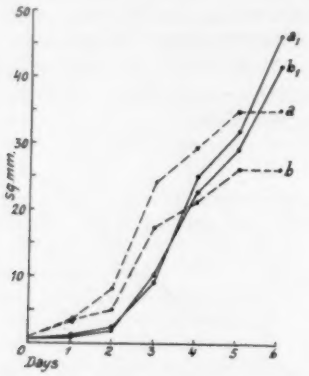

Fig. 3 (patient Miz.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by a and a_1 and b and b_1.

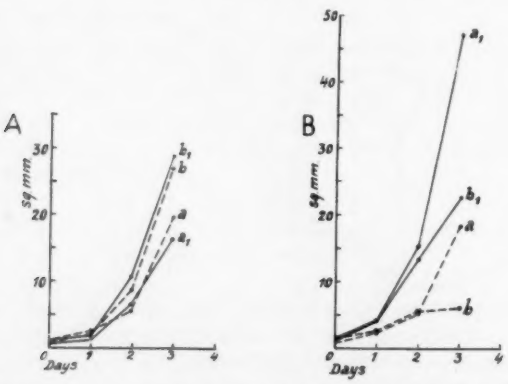

Fig. 4 (patient Sh.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by a and a_1 and b and b_1. A and B represent two sets of cultures.

Experiment 2.: A 52 year old patient (Sh.) was in a uremic state resulting from chronic nephritis. The content of urea in the blood was 272 mg. per hundred cubic centimeters and that of uric acid 12.6 mg.

The effect of the serum of this patient on cultures stimulated with embryonic extract was examined. The liquid phase of the medium of the test flasks consisted of 0.5 cc. of the patient's serum and 0.5 cc. of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration and the same quantity of normal human serum. The growth curves of both pairs of cultures are shown in figure 4*A* and *B*.

Results: The addition of uremic serum had no injurious effect on the growth of fibroblasts. Occasionally growth stimulation was observed. The appearance of the proliferating cells was entirely normal.

EXPERIMENT 3: A 52 year old patient (Sch.) was suffering from arteriosclerotic, contracted kidney with uremia. The content of urea in the blood was 356 mg. per hundred cubic centimeters and that of uric acid 11.2 mg.

The effect of the serum of this patient was tested on cultures stimulated with embryonic extract and on nonstimulated cultures. In the experiments on stimulated cultures the liquid phase of the medium of the test flasks consisted of 0.5 cc.

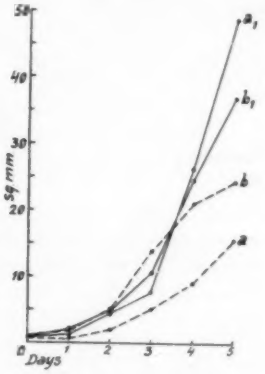

Fig. 5 (patient Sch.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by a and a_1 and b and b_1.

of the patient's serum and 0.5 cc. of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration and the same quantity of normal human serum. The growth curves are shown in figure 5. In the experiments without addition of embryonic extract the liquid phase of the medium of the test flasks consisted of 1 cc. of the patient's serum, while the control flasks contained 1 cc. of normal human serum. The growth curves of these cultures are shown in figure 6*A*, *B* and *C*.

Results: The cultures with or without embryonic extract grew with the addition of uremic serum better than those with normal serum. The proliferating cells had an entirely normal appearance.

EXPERIMENT 4: A 68 year old man (F.) was suffering from uremia of unknown cause. The content of urea in his blood was 380 mg. per hundred cubic centimeters.

The effect of the serum of this patient on cultures stimulated with embryonic extract and on nonstimulated cultures was tested. In the experiments on stimulated

cultures the liquid phase of the medium of the test flasks consisted of 0.5 cc. of the patient's serum and 0.5 cc. of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration and the

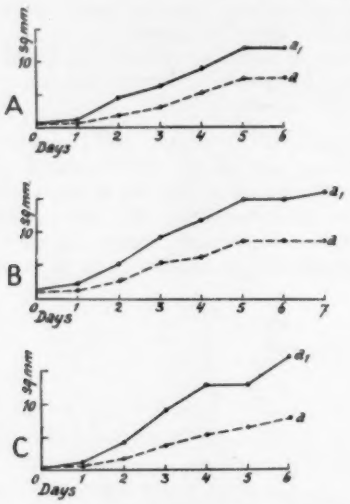

Fig. 6 (patient Sch.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line). Sister cultures are designated by a and a_1 and b and b_1. *A*, *B* and *C* represent three sets of cultures.

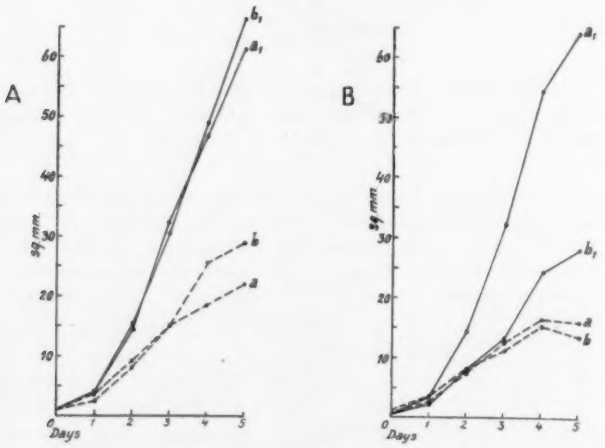

Fig. 7 (patient F.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by a and a_1 and b and b_1. *A* and *B* represent two sets of cultures.

same quantity of normal human serum. The growth curves are shown in figure 7*A* and *B*. In the experiments on nonstimulated cultures the liquid phase of the medium of the test flasks consisted of 1 cc. of the patient's serum, while the control flasks contained 1 cc. of normal human serum. The growth curves of these cultures are shown in figure 8.

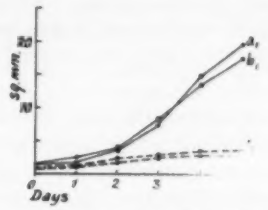

Fig. 8 (patient F.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line). Sister cultures are designated by *a* and a_1 and *b* and b_1.

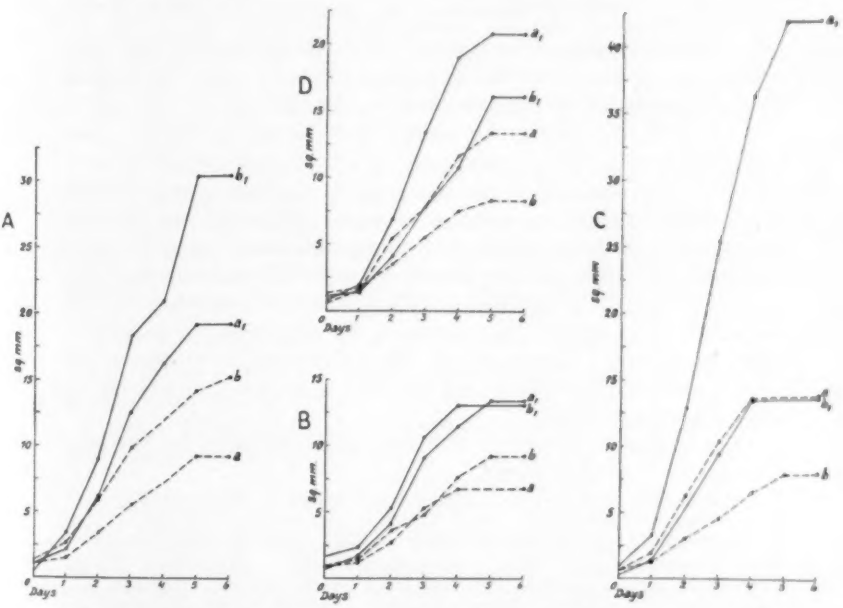

Fig. 9 (patient R. Sh.).—Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line). Sister cultures are designated by *a* and a_1 and *b* and b_1. *A*, *B*, *C* and *D* represent four sets of cultures.

Results: In all experiments, with or without addition of embryonic extract, the uremic serum had a stimulating effect on growth. The proliferating cells had an entirely normal appearance.

EXPERIMENT 5: A 43 year old woman (R. Sh.) was suffering from severe renal insufficiency caused by chronic nephritis. The content of urea in the blood at the time of the experiment was 245 mg. per hundred cubic centimeters.

The effect of the serum of this patient was tested on nonstimulated cultures. The liquid phase of the medium of the test flasks consisted of 1 cc. of the patient's serum, while the control flasks contained 1 cc. of normal human serum. The growth curves of the cultures are shown in figure 9*A*, *B*, *C* and *D*.

Results: The addition of the uremic serum in this case resulted in considerable stimulation of growth in all experiments. The proliferating cells had an entirely normal appearance.

In summary of the results of the experiments with uremic serum, it may be concluded that uremic serum added to cultures of fibroblasts had no injurious effect on the cells or inhibitory influence on the growth of the cultures. Morever, it may have had a certain stimulating effect on cell proliferation.

EFFECT OF UREMIC URINE ON GROWTH OF FIBROBLASTS IN VITRO

It was shown in a previous report [9] that normal human urine added to cultures of fibroblasts has a definite injurious effect on growth. The addition of higher concentrations of urine (1 and 0.5 cc.; specific gravity, 1.026 to 1.030) to the usual contents of the flask causes complete inhibition of cell proliferation. Smaller concentrations of urine inhibit the growth rate of the cell colonies, the degree of inhibition being parallel to the concentration of urine. When 0.25 cc. of urine was added a barely perceptible growth was observed. After the addition of 0.1 cc. there was appreciable growth, but distinctly less than in the controls. The inhibition of growth was also generally noticeable with 0.05 cc. of urine. The method of demonstrating the toxicity of urine by its effect on the growth rate of colonies of fibroblasts has proved exceedingly sensitive and provided a quantitative method for measuring urinary toxicity.

This method was used in the following experiments to determine the toxicity of uremic urine.

The urines of 4 uremic patients were tested in this manner.

EXPERIMENT 1: A 52 year old patient (S. H.) was in a uremic state from arteriosclerotic, contracted kidney. The content of urea in the blood was 272 mg. per hundred cubic centimeters. The maximum specific gravity of the urine was 1.006.

Urine of this specific gravity was added to the test flasks as the liquid phase of the medium. The growth of cultures in these flasks was compared with the growth of their sister cultures in the control flasks, containing Tyrode's solution as the liquid phase of the medium.

9. Rachmilewitz, M.: Toxic Effect of Human Urine on Fibroblasts Growing in Vitro, Proc. Soc. Exper. Biol. & Med. **43**:497, 1940.

Results: After the addition of 1 cc. of urine only slight growth was observed. A noticeable inhibition of growth was also seen when 0.5 cc. of urine was added.

EXPERIMENT 2: A 50 year old patient (R.) had a clinical diagnosis of malignant hypertension with uremia. The content of urea in the blood was 195 mg. per hundred cubic centimeters. The maximum specific gravity of the urine was 1.014. The experiment was carried out under the same conditions as the preceding one.

Results: There was no growth either with 1 cc. or with 0.5 cc. of urine.

EXPERIMENT 3: A 43 year old patient (R. S.) had a clinical diagnosis of chronic nephritis with uremia. The content of urea in the blood was 102 mg. per hundred cubic centimeters. The maximum specific gravity of the urine was 1.010. The experimental conditions were those of experiments 1 and 2 in this group.

Results: There was a complete inhibition of growth with the addition of 1 cc. of urine. The occurrence of single cells or considerable inhibition of growth was observed with 0.5 cc. of urine. Distinct inhibition of growth was noticed with 0.25 cc. of urine.

EXPERIMENT 4: A 26 year old patient (V. M.) had a clinical diagnosis of chronic nephritis and preuremia. The content of urea in the blood was 56 mg. per hundred cubic centimeters. The maximum specific gravity of the urine was 1.010. The experimental conditions were those of experiments 1 and 2 of this group.

Results: Complete inhibition of growth was observed with the addition of 1 cc. of urine.

EXPERIMENT 5: In another experiment the urine of the patient just mentioned (V. M.) was tested against normal urine of the same specific gravity (1.010).

Results: When 1 cc. of urine was added there was complete inhibition of growth of the test cultures as well as of the control cultures. With 0.5 cc. of urine there was extreme inhibition of growth, and with 0.25 cc., less but definite inhibition of growth of both the test and the control culture.

The experiments have thus shown that the uremic urine, though of low specific gravity, has an extremely injurious and inhibitory effect on fibroblasts growing in vitro.

Uremic urine showed the same degree of toxicity as normal urine of the same concentration.

COMMENT

The fact which I previously demonstrated, that normal human urine contains substances which have a toxic effect on cells in vitro, raised the problem whether these cell-damaging substances are retained in the blood of uremic patients, and, thus, may have a bearing on the symptom complex of uremia. The examination of this possibility was carried out in the reported experiments.

Investigation was made to determine two things: (1) whether the cell-damaging effect of uremic urine was lessened through the retention of the toxic substances concerned and (2) whether the retention of these substances resulted in their accumulation in the blood.

The experiments have shown that the cell-toxic effect of uremic urine does not differ from that of normal urine and that these cell-toxic substances could not be demonstrated in uremic blood in effective concentrations. The two observations are in accord.

Results obtained on a definite test object, in this instance the cell culture, obviously cannot be related without reservation to the complicated mechanism of the entire human body. With such reservation in mind, it can be stated in any case that the urinary substances which are definitely toxic for the cell in vitro are not retained in uremic blood, at least not in effective concentrations.

The lack of toxic effect of uremic serum on cells cultivated in vitro is not surprising in the light of the modern concept of the pathogenesis of uremia. The variability of the clinical symptoms of uremia alone speaks against the assumption that the uremic symptom complex can be related to accumulation in the blood of a single toxic substance. Various factors are considered responsible for the production of the clinical picture of uremia. Even Volhard, who stressed the significance of retained phenols for the causation of uremic symptoms, assumed that the clinical picture of uremia could be more fully explained by indirect toxic action than by the direct effect of one particular poison. The muscular irritability occasionally observed in patients suffering from uremia may serve as an example of indirect toxic effect caused by the lowering of the calcium content of the blood secondary to retention of phosphates. Likewise, urea, a substance of relatively low toxicity, may be indirectly toxic in at least two ways: 1. Urea may increase penetration into the body cells of potentially toxic substances (Baur [10]). 2. Together with other retained excretory products, urea may interfere with detoxifying mechanisms of the body, leading to accumulation of substances which normally occur only in traces (Fishberg). Thus, Mason and his co-workers have shown that previous injections of urea in dogs caused a definite delay in disappearance from the blood stream of administered guanidine.

It is thus possible that in the production of uremic symptoms an important role can be ascribed to the accumulation of toxic substances in the tissues and to disturbances of cellular activity of various organs rather than to toxins circulating in the blood.

Another evidence of the low toxicity of uremic blood has been given by Russian workers, who have used uremic blood for transfusion in human beings and in animals (Veselkin and Kapica [11]). They could not

10. Baur, M.: Zur Pharmakologie des Harnstoffs (Beiträge zum Problem der Urämie), Arch. f. exper. Path. **167**:104, 1932.

11. Veselkin, P. N., and Kapica, L. M.: Experimental Observations Concerning Transfusion of Uremic Blood, Vestnik chir. **48**:9, 1936.

observe any untoward effects of the uremic blood. Moreover, because of its effect on the coagulation of blood, they have recommended its use to stop bleeding in hemorrhagic conditions.

The last point to be discussed is the stimulating effect of uremic serum on the growth rate of the fibroblast cultures observed in some of the experiments. Since Carrel's classic studies concerning the growth-promoting factors in tissue culture, it is known that intermediary protein metabolites (proteoses) stimulate cell multiplication. Recently it has been found that allantoin, a derivative of purine, stimulates the healing process of deep purulent wounds. Urea was found to be even more effective than allantoin. Since urea may be obtained from allantoin by hydrolysis, Hetherington and Shipp [12] expressed the opinion that the growth-promoting effect of allantoin might be due to the urea and not to allantoin itself. However, while they could demonstrate the stimulating effect on fibroblast cultures when allantoin was added to the medium, they failed to observe the same effect with urea.

The available evidence does not permit a conclusive definition of the substance in the uremic serum which is responsible for the stimulation of growth, but it is well justified to assume that this effect is caused by retained products of intermediary protein metabolism.

SUMMARY

Fibroblast colonies were used as the test object to examine the toxicity of uremic serum and urine. The experiments have shown that uremic serum added to the medium has no injurious or inhibitory effect on the growth of fibroblasts. Stimulation of growth was observed with some uremic serums, with a high content of urea as compared with that of normal serums. Urine from uremic patients interferes with growth of fibroblasts in vitro, as does normal urine. The significance of these experiments in relation to the problem of uremia is discussed.

12. Hetherington, D. C., and Shipp, M. E.: Effect of Urea upon Growth of Fibroblasts from Cardiac Explants in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **37**:238, 1937.

INFARCTION OF THE LUNG

A CLINICAL AND ROENTGENOLOGIC STUDY

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The clinical recognition of pulmonary infarction in many instances is difficult. This is illustrated by the fact that in only 22 per cent of our cases was the condition diagnosed correctly ante mortem. This study was made in an attempt to correlate the clinical and roentgenologic data with the pathologic observations and thus improve our diagnostic accuracy.

From Jan. 1, 1930 to Dec. 31, 1939 6,548 autopsies were performed at Cleveland City Hospital. Among these were found 344 instances of aseptic hemorrhagic infarction of the lung, an incidence of 5.2 per cent. In 174 of these 344 cases the infarct was considered to be the major cause of death or an important contributory factor. The infarct was considered significant if it was 5 cm. in size or larger. Multiple infarcts, even if smaller, were considered significant. However, even if it was large, the infarct was classified as unimportant if another adequate cause of death existed, for example, generalized peritonitis or carcinomatosis. In addition, an infarct, regardless of its size, was considered significant if its onset coincided with a definite change for the worse in the course of the patient's illness. On the basis of these criteria, pulmonary infarct was found to be a significant cause of death in 174 instances, or 2.7 per cent of our postmortem material.

Belt,[1] studying a series of 1,990 consecutive autopsies, found 155 instances of hemorrhagic infarct of the lung, excluding cases of septicemia, an incidence of 7.8 per cent. Hampton and Castleman,[2] in 3,500 autopsies at Massachusetts General Hospital, found pulmonary embolism or infarction in 315 cases, or 9 per cent.

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1. Belt, T. H.: The Aetiology of Lung Infarction, Brit. Heart J. **1**:283-289 (Oct.) 1939.

2. Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Teleoroentgenograms with Autopsy Findings, Am. J. Roentgenol. **43**:305-326 (March) 1940.

SOURCE OF THE THROMBUS IN THE PULMONARY ARTERY

An attempt was made to determine the origin of the thrombus in the pulmonary artery from a study of the clinical records and autopsy protocols. This was not successful, since in 54 per cent of the cases no source could be found. One cannot infer that in these cases the thrombus originated in the pulmonary artery, although in many of them it may have done so. In the majority of instances the extremities were not examined, and in other cases the protocols were not complete. Belt [1] and Gsell [3] stated that in most of the cases they reported the infarct was embolic in origin. However, Roubier [4] expressed the belief that infarction most frequently followed local thrombosis, presumably because of slowing of the circulation. This opinion may be due to the fact that the underlying cause of death in all of the cases he reported was heart disease.

SITE OF THE INFARCT

Many authors have noted that the lower lobe, especially of the right lung, is the most frequent site of infarction. Such a distribution was also found in our material. The lower lobe of the right lung was the only lobe involved in 27 per cent of the cases, and the lower lobe of the left lung in 15 per cent. However, the lower lobe of the right lung alone or in combination with other lobes was the site of an infarct in 69 per cent of the cases, and the lower lobe of the left lung alone or with other lobes, in 53 per cent. The remaining lobes were rarely involved alone.

INFARCT AND HEART DISEASE

In Hosoi's [5] group of 25 cases of postoperative embolism, in 12 of which pulmonary infarction occurred, it was noted that a large heart was present in 9. In the 1,990 cases with autopsy analyzed by Belt,[1] there were 235 instances of death from heart disease. In 70 of these cases pulmonary infarction was present. In 52, gross cardiac failure antedated the infarct.

Levine and White [6] found 22 instances of pulmonary infarction in 62 cases of hypertensive and rheumatic heart disease in which gross

3. Gsell, O.: Hemorrhagic Pulmonary Infarction and Its Complications, Deutsche med. Wchnschr. **61**:1317-1320 (Aug. 16) 1935.

4. Roubier, C.: Comparative Frequency and Pathogenesis of Pulmonary Infarcts in Different Cardiopathies, Lyon méd. **162**:181-189 (Feb. 12) 1939.

5. Hosoi, K.: Pulmonary Embolism and Infarction, Ann. Surg. **95**:67-72 (Jan.) 1932.

6. Levine, H. B., and White, P. D.: Pulmonary Infarction Complicating Severe Diseases of the Mitral Valve, Arch. Int. Med. **60**:39-50 (July) 1937.

cardiac failure occurred. In a parallel group of 72 cases in which there was no cardiac failure there were only 7 cases of infarct.

McCartney [7] stated that the incidence of pulmonary infarction, occurring postoperatively, doubled when heart disease was present.

Of 241 cases in our material in which there was heart disease and pulmonary infarction, irrespective of the presence of cardiac failure, the infarct was an important cause of death in 157, or 65 per cent. Of 103 cases in which there was no heart disease, the infarct was significant in only 17, or 16 per cent (table 1). The latter group included 21 cases of postoperative infarction, in only 5 of which the infarct was large.

PLEURAL EFFUSION

Gsell [8] noted the presence of a pleural effusion in one half of his patients who had a pulmonary infarct. He cited Krehl's statement that

TABLE 1.—*Incidence of Infarction and Cardiac Disease in Three Hundred and Forty-Four Cases*

Cases of cardiac disease and pulmonary infarct.....	241		
Infarct significant as a cause of death.....		157	65%
Infarct only incidental.....		84	35%
Cases of infarct without cardiac disease.....	103		
Infarct significant as a cause of death.....		17	16%
Infarct only incidental.....		86	84%
		344	

an obstinate, seemingly primary, serous pleural effusion in a patient with heart disease is often due to infarct. In this respect the data from our material was difficult to evaluate. In a large number of cases there was pleural effusion, but in many there was also cardiac failure. From a study of the charts alone it was often impossible to determine whether the infarct preceded the fluid. However, there were a number of instances in which this sequence was definite, and in a few instances hydrothorax developed without evidence of heart disease.

In most cases the effusion was serous, although in some it was serosanguineous. In others the notation was made that bile pigments were present. The presence of such substances in pleural effusion due solely to cardiac failure is unusual, since the fluid is a pure transudate and should not contain bile pigments.

7. McCartney, J. S., cited by Barnes, A. R.: Pulmonary Embolism, J. A. M. A. **109**:1347-1353 (Oct. 27) 1937.

CLINICAL OBSERVATIONS

In 73 of the 174 cases in which the infarct was a significant cause of death, the clinical observations could be correlated with those made at postmortem examination. These data are summarized in table 2. Hemoptysis, often repeated, with the blood usually bright red and of small amount, was the most frequently noted symptom. Pain and an increase in dyspnea were next in frequency. The usual physical signs were those of consolidation and pleural effusion. Pleural friction rubs were occasionally heard.

Bullowa [8] and Lord and Hefron [9] stated that a chill might occur in association with pulmonary infarction, but the latter authors stated the opinion that it was less common than in lobar pneumonia. Gsell [3] found an initial chill to be present in only 1 per cent of his 200 cases. The latter observation is in accord with our experience, since in none of the 73 cases was a history of a chill elicited.

TABLE 2.—*Occurrence of Signs and Symptoms in Seventy-Three Cases*

Hemoptysis	48	65%
Rales	48	65%
Pain	25	32%
Dulness	23	31%
Dyspnea (increase in)	22	30%
Bronchial breath sounds	15	20%
Friction rub	9	12%
Cough, no hemoptysis	5	7%

In 55 of these 73 cases there was clinical evidence that the infarct had occurred within the last twelve days of life. In 23 cases the infarct was followed by death in three days or less. The approximate age of the infarct was consistent with the history in all 73 cases. This short interval between the occurrence of a pulmonary infarct and death indicates that this complication carries a grave prognosis.

On the same day that the infarct made itself evident there was an average increase in the temperature of 1.5 C. (2.7 F.). The pulse rate increased 20 beats per minute and the respiratory rate 8 per minute.

Icterus, which is usually considered a common accompaniment to pulmonary infarction, was noted in some cases. Its occurrence, however, was not sufficiently frequent to permit evaluation of its significance, especially since another possible cause of icterus was often present, namely, severe passive hyperemia of the liver.

8. Bullowa, J. C.: The Management of the Pneumonias, New York, Oxford University Press, 1937.

9. Lord, F. T., and Hefron, R.: Pneumonia and Serum Therapy, New York, The Commonwealth Fund, 1938.

There were several cases in this series in which a secondary abscess developed in the infarct, with a bronchopleural fistula and empyema. In this group expectoration of foul purulent sputum was present. This interesting group is being studied in detail and will be reported later.

ROENTGENOLOGIC OBSERVATIONS

A number of authors, including Kirklin and Faust,[10] Levy,[11] Jellen,[12] Westermark,[13] Smith [14] and Hampton and Castleman,[2] have discussed the roentgenologic findings in pulmonary infarction. All stressed the varied appearance of the infarcts, depending on their size, position and age and the presence of secondary infection, passive hyperemia or pleural effusion. In general, it has been noted that the typical postmortem appearance of a triangular infarct, situated in a lower lobe, is the exception rather than the rule in the roentgenogram, unless exposures are made in more than one projection. This variation in the shadow is due to the fact that unless the roentgen rays pass at right angles to the infarct, the shadow will be ovoid, rather than triangular. If they pass through the infarct in its long axis, the shadow will be round. The finding of a round shadow has been responsible for at least one attempted pneumonectomy for supposed tumor of the lung.[15]

The density of the shadow is usually less than that seen in lobar pneumonia, since less of the lung is involved. The shadow will change little in twenty-four hours, whereas in the early stages of lobar pneumonia the shadow may show an extensive spread.

At times the appearance is only that of a hazy horizontal streaking at the base, usually with some elevation of the diaphragm. This streaking may simulate localized patches of atelectasis. The hilar shadows are usually accentuated, although the passive hyperemia which is often present may account for this appearance. However, Westermark [13] made the

10. Kirklin, B. R., and Faust, F. S.: A Clinical and Roentgenologic Consideration of Pulmonary Infarction, Am. J. Roentgenol. **23**:265-275 (March) 1930.

11. Levy, H.: Atypical Roentgen Appearance of Pulmonary Infarction in Patients with Heart Failure, Am. J. Roentgenol. **35**:635-639 (May) 1936.

12. Jellen, J.: The Roentgenological Manifestation of Pulmonary Embolism with Infarction of the Lung, Am. J. Roentgenol. **41**:901-908 (June) 1939.

13. Westermark, N.: On Roentgen Diagnosis of Lung Embolism, Acta radiol. **19**:357-372, 1938.

14. Smith, K. S.: The Radiology of Pulmonary Infarction, Quart. J. Med. **7**: 85-99 (Jan.) 1938.

15. Coste, F., and Bolgert, M.: Round Roentgen Image Due to White Infarction Resulting from Endarteritis, Bull. et mém. Soc. méd. d. hôp. de Paris **57**:1362-1368 (Nov. 27) 1933.

interesting observation that if roentgenograms were made within an hour or two of the occlusion of the branch of the pulmonary artery, an area of avascularity in the pulmonary field was noted. This same area later showed an increase in density, due to the infarct which followed.

Secondary bronchopneumonia may occur, causing edges of the shadow to appear feathery, rather than well defined. The development of a pleural effusion may obscure the infarct entirely. Secondary abscess formation, with or without the development of a bronchopleural fistula and empyema, may occur. This complication will further obscure the picture, particularly if the patient is not seen until the late stages of his illness.

Even a small infarct may leave a shadow which persists for many months, or even years. The residual shadow resembles streaks of fibrous tissue. Such a shadow has been noted in some of our cases (not included in the statistical series) in which the patients have recovered.

The shadow of an infarct must be differentiated from that seen in cases of lobar pneumonia, bronchopneumonia, abscess, neoplasm, cyst, passive hyperemia and interlobar effusion.

Examples of the different types of shadows and brief case histories are included in this report.

DIAGNOSIS

While the difficulties interposed by the presence of cardiac failure are recognized, it is evident that the diagnosis of infarction will be made only as often as the condition is thought of and looked for clinically. The classic symptoms of hemoptysis, thoracic pain, dyspnea and fever and the physical signs indicating involvement of the lung and the overlying pleura should point to such a diagnosis. In addition, the presence of a persistent pleural effusion, especially if bile pigments are present, in a patient with cardiac failure, together with an otherwise unexplained fever should suggest the diagnosis of an infarct underlying the effusion, even if the classic symptoms are absent. That unexplained fever may often be due to an infarct was mentioned by Kinsey and White,[16] who studied the occurrence of fever in cases of congestive heart failure. They found pulmonary infarction present in 24 out of 50 cases in which autopsy was performed. All of the patients had had an unexplained fever during their stay in the hospital.

The appearance of the roentgenograms may be of great help if they are taken before a pleural effusion obscures the pulmonary fields and

16. Kinsey, D., and White, P. D.: Fever in Congestive Heart Failure, Arch. Int. Med. **65**:163-170 (Jan.) 1940.

if the varied appearance of the infarcts is borne in mind. Roentgenograms taken in more than one projection will often clarify the problem.

However, of our series of 174 cases of significant pulmonary infarct, in only 22 per cent was the condition correctly diagnosed clinically. In 28 per cent it was called bronchopneumonia. In 50 per cent no diagnosis of any pulmonary lesion other than passive hyperemia was made. Roubier [4] and others have reported similar experiences.

Clinically, pulmonary infarct must be differentiated from pneumonia. The presence of bacteria, especially pneumococci, in the sputum or blood and a prompt response to specific serum therapy or chemotherapy would favor the diagnosis of pneumonia. The absence of a chill, the rapid accumulation of a pleural effusion and an increase in the signs of cardiac failure would point to the presence of an infarct.

Right hydrothorax is a frequent occurrence in cases of cardiac failure. The fact that infarction of the lung occurs so much more frequently on the right side and by itself can cause a pleural effusion may in part explain this well known observation.

REPORT OF FIVE CASES

CASE 1.—F. B., a white man aged 28, known to have rheumatic heart disease with mitral stenosis, was admitted to the medical service on Feb. 11, 1940 in a condition of moderately severe cardiac failure. The course of his illness was satisfactory until the twenty-eighth day of hospitalization, when he expectorated a small amount of blood. On the thirty-second day he again had hemoptysis, together with a pleuritic pain on the right side. Two days later, after the removal of 400 cc. of serosanguineous fluid from the right pleural space, a roentgenogram revealed an ovoid area of increased density in the upper lobe of the right lung (fig. 1 *A*). The next day an examination with the patient in the second oblique position showed the shadow to be slightly more dense, well defined, triangular and anterolateral in position, just above the interlobar septum (fig. 1 *B*).

Small daily hemoptyses continued. On the fortieth day the patient's sputum was found to be purulent and foul, and examination revealed right pneumothorax. The latter observation was confirmed by a roentgenogram, which also revealed a fluid level in the pleural space, an area of diminished density in the upper lobe of the right lung and a dense shadow opposite the left hilus. The last was thought to represent another infarct (fig. 2). The patient died that evening, twelve days after his first hemoptysis.

Autopsy revealed rheumatic heart disease with mitral stenosis, mural thrombi in the right atrium and emboli in several branches of the pulmonary artery. In the upper lobe of the right lung was a moderately fresh infarct in the position indicated by the roentgenograms, with necrosis in the center, a bronchopleural fistula and a seropurulent effusion (fig. 3). In the lower lobe of the right lung there were two large infarcts, with abscess formation but without communication with the pleural space. There was a large fresh infarct in the upper lobe of the left lung.

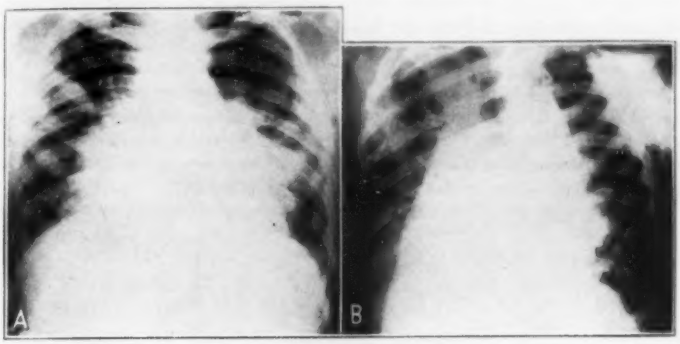

Fig. 1 (case 1).—*A*, roentgenogram taken March 21, 1940. The cardiac shadow is enlarged and has a straight-line border. The increased density of the hilar markings indicates the presence of passive hyperemia. Just above the interlobar septum on the right side there is a sharply demarcated ovoid shadow, which represents the infarct in the upper lobe of the right lung. *B*, roentgenogram made March 22, with the patient in the second oblique position. The shadow is triangular and lies anteriorly in the upper lobe of the right lung at the interlobar septum.

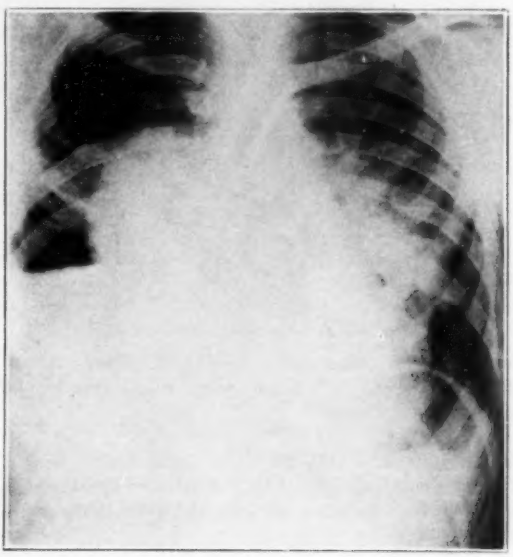

Fig. 2 (case 1).—Roentgenogram taken March 26, 1940. Pneumothorax is present on the right, with a pleural effusion and some adhesion bands. Apparent "honeycombing" in the collapsed upper lobe of the right lung indicated probable formation of an abscess. There is a dense shadow, which proved to be an infarct, opposite the lower portion of the left hilus.

This case illustrates the variation in the appearance of the shadow of the infarct in different projections and also the development of a bronchopleural fistula with empyema, obscuring the infarct entirely.

CASE 2.—J. Z., a white man aged 70, was admitted to the surgical service on March 13, 1939 for a lumbar sympathectomy, because of peripheral vascular disease. On the fifth day after operation, pain developed in the left upper quadrant of the abdomen and the patient had a small hemoptysis. A roentgenogram (fig. 4*A*) taken the next day showed streaked shadows in the lower lateral

Fig. 3 (case 1).—A section through the fixed right lung shows the infarct, with necrosis in the center. The arrow points to the communication between the abscess and the pleural space.

portion of the left pulmonary field, the whole streaked area being ovoid. Four days later a lateral view of the chest (fig. 4*B*) showed the infarct to be situated posteriorly in the lower lobe of the left lung and to be triangular. The patient died on the twelfth day after operation, seven days after the infarct occurred.

Postmortem examination confirmed the diagnosis of an infarct in the lower lobe of the left lung and revealed the lesion to be 5 cm. in length. Several more recent, smaller infarcts were also present.

This case illustrates that the triangular shape of the infarct may be revealed in projections other than the conventional posteroanterior one.

CASE 3.—D. W., a woman aged 57, was admitted in a moribund state to the medical service on March 23, 1939. Physical examination revealed consolidation of the lower lobe of the right lung, thrombophlebitis in the region of the right ankle and cellulitis of the right forearm. A roentgenogram (fig. 5) revealed a few streaks of increased density, horizontal in position, just above the right half of the diaphragm, which was elevated. These streaks suggested localized patches of atelectasis. A diagnosis of septicemia was made and sulfanilamide was administered, but the patient died twenty-six hours after admission.

Autopsy revealed acute bacterial endocarditis, due to Streptococcus haemolyticus, and recent infarcts of the lower lobe of the right lung, just above the diaphragm.

In spite of the fact that the roentgenogram in this case was taken within a few hours of death and that well defined infarcts were found at autopsy, the roentgenogram revealed only a few horizontal streaks of increased density, suggesting localized plaques of atelectasis.

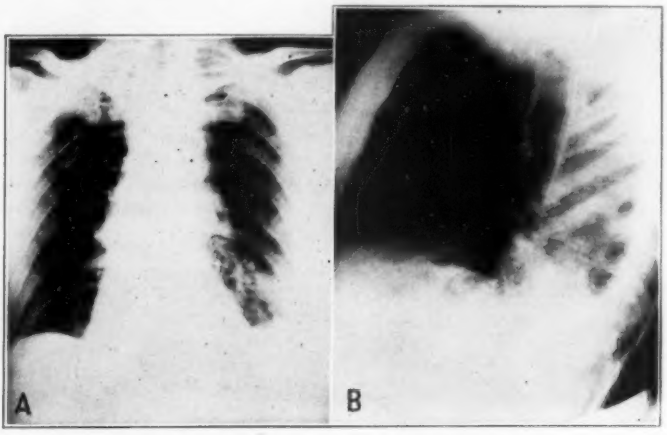

Fig. 4 (case 2).—*A*, an ovoid area of increased density, streaked in appearance, in the lower lateral portion of the left pulmonary field. The left half of the diaphragm is elevated. Considerable emphysema is present. *B*, left lateral view of the chest as seen in a roentgenogram taken four days after that shown in figure 4 *A*. A definitely triangular area of increased density is located posteriorly in the lower lobe of the left lung.

CASE 4.—A. J., a white girl aged 16, was admitted to the medical service on May 5, 1939, with the diagnosis of rheumatic pancarditis. Four days before admission she had had a small hemoptysis and some pain in the right side of the chest. Both recurred daily until the third day of hospitalization, at which time a roentgenogram (fig. 6) of the chest revealed an enlarged cardiac shadow, with a mitral configuration. Great accentuation of the hilar shadows indicated the presence of severe passive hyperemia. No infarcts were seen.

The patient died May 19, the fourteenth day of hospitalization, and postmortem examination revealed a large organizing infarct in the lower lobe of

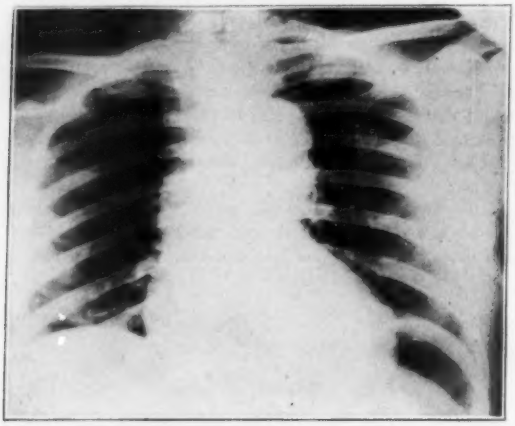

Fig. 5 (case 3).—An anteroposterior view of the chest, as seen in a roentgenogram taken with the patient recumbent, shows a few streaks of increased density parallel to and just above the right half of the diaphragm. At autopsy a few hours later, a fresh but well demarcated infarct was present in this location.

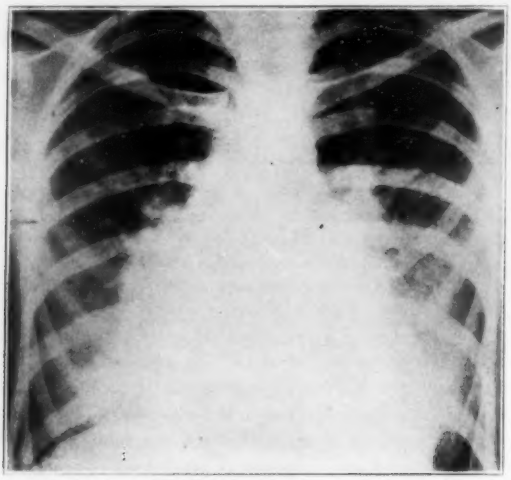

Fig. 6 (case 4).—The cardiac shadow is seen to be enlarged, and the left cardiac border is convex. A large amount of passive hyperemia is present, as evidenced by an increase in density of the hilar shadows. Although definite infarcts were present in the right lung at autopsy and were undoubtedly present at the time this roentgenogram was made, a diagnosis cannot be made.

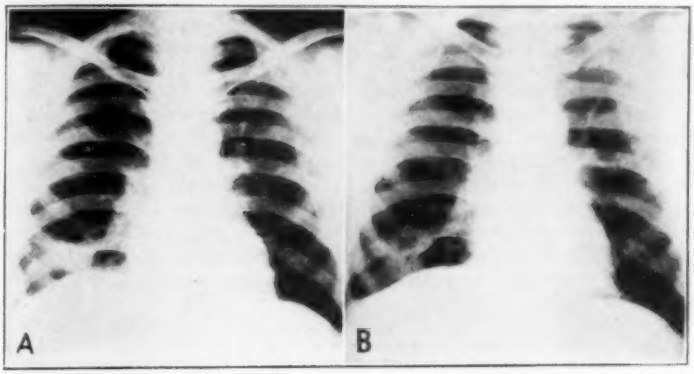

Fig. 7 (case 5).—*A*, posteroanterior view of the chest in a roentgenogram made on the day of admission, four days after the first hemoptysis, shows a rounded shadow of increased density in the lower portion of the right pulmonary field just above the diaphragm. There is a slight haziness beside and below this shadow. *B*, in a roentgenogram made two months later the round shadow is less dense and is sharply demarcated. Some retraction at its upper border is due to partial healing and to replacement by scar tissue.

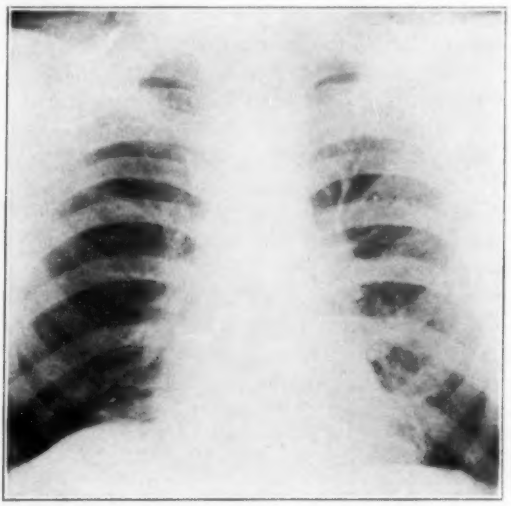

Fig. 8 (case 5).—Two years later the shadow in the lower portion of the right lung has been replaced by a stellate scar of fibrous tissue. Lobar pneumonia would not leave such a residual scar; by this criterion the two processes may be differentiated.

the right lung, and many smaller, more recent infarcts in the remainder of the right lung.

The infarct, which was present in the lower lobe of the right lung at the time the roentgenogram was made, was, despite its size, obscured by the passive hyperemia and the large cardiac shadow.

CASE 5.—F. Y., a white man aged 49, was admitted to the medical service on Feb. 8, 1938. Four months before admission he had sustained a fracture of the right tibia. The right leg had been placed in a cast for about one month. Nineteen days before admission severe pain developed in the right side of the chest, and two days later the patient had a small hemoptysis, with some streaking of the blood, which recurred until the time of admission. Four days before admission he noticed swelling of the right leg. On admission there were signs of consolidation in the lower lobe of the right lung and of thrombophlebitis in the right thigh. A roentgenogram made at this time revealed an ovoid shadow of increased density, with slightly feathered edges (fig. 7 *A*).

After a prolonged period of elevated temperature the physical signs in the lung and the thrombophlebitis subsided. A roentgenogram made on the fifty-sixth day of hospitalization (fig. 7 *B*) showed the same shadow, of the same size but of less density. Some streaked fibrous changes were noted. The patient was discharged, asymptomatic, on the eighty-second day.

Two years later another roentgenogram of the chest (fig. 8) showed a stellate scar in the same area, just above the right half of the diaphragm. This scar tissue represented the final healing of the infarct and illustrates the fact that pulmonary infarct, unlike lobar pneumonia, will often leave a scar which will persist for years.

SUMMARY AND CONCLUSIONS

In 6,548 cases in which autopsy was done, 344 cases of aseptic hemorrhagic infarction of the lung were observed, an incidence of 5.2 per cent.

In 174 instances, or 2.7 per cent, the pulmonary infarct was a significant cause of death.

Infarction is a far more serious complication in the course of heart disease than in its absence.

Hemoptysis is the most frequently noted symptom. The physical signs vary considerably and are modified by the presence of secondary infection or pleural effusion.

There is no single typical roentgenologic picture of pulmonary infarction. Roentgenograms taken in more than one projection will aid considerably in making the diagnosis.

In our series a correct diagnosis was made in 22 per cent of the cases in which the infarct was an important cause of death.

THE COLD PRESSOR AND THE BREATH-HOLDING TEST

AN ANALYSIS OF RESULTS IN TWO HUNDRED SUBJECTS

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Blood pressure rises in response to many stimuli in both normal and hypertensive persons. It is well known that the response is greater in patients with essential hypertension than it is in normal persons. In an attempt to devise a standard stimulus for measuring this reaction, Hines and Brown [1] developed the cold pressor test.

More recently Ayman and Goldshine [2] described a breath-holding test for use as a standard blood pressure stimulus. They concluded that there was a "striking similarity" in the reactions of the blood pressure to the cold pressor and breath-holding tests. In their series the breath-holding test, as a general rule, showed a greater reaction. Since the breath-holding test requires no special equipment, Ayman and Goldshine felt it might well be used in place of the cold pressor test. In order to compare the two tests, the reactions of 200 persons, some with normal and some with elevated blood pressures, have been observed.

TECHNIC OF TESTS

The exact technic of Hines [3] was used for the cold pressor test. The subject reclined in a quiet room for a period of twenty to sixty minutes. Blood pressure determinations were made at intervals until a basal level was reached. A longer rest period is usually required in hypertensive patients. The cuff of the sphygmomanometer remained on one arm, and after the basal level was reached, the opposite hand was plunged into water at a temperature of 3 to 5 C. (37.6 to 41 F.). The hand was kept immersed to just above the wrist for sixty seconds. The blood pressure was determined at thirty seconds and sixty seconds.

After the cold pressor test was finished, and the blood pressure had returned to the basal level, the breath-holding test was given. The only deviation from

From the Medical Department, Northwestern Mutual Life Insurance Company.

1. Hines, E. A., Jr., and Brown, G. E.: A Standard Stimulus for Measuring Vasomotor Reactions, Proc. Staff Meet., Mayo Clin. **7**:332 (June 8) 1932.

2. Ayman, D., and Goldshine, A. D.: The Breath-Holding Test: A Simple Standard Stimulus of Blood Pressure, Arch. Int. Med. **63**:899 (May) 1939.

3. Hines, E. A., Jr.: Technic of the Cold Pressor Test, Proc. Staff Meet., Mayo Clin. **14**:185 (March 22) 1939.

the technic of Ayman and Goldshine was that the subject was kept in a supine position throughout the test instead of the sitting position. The subject was instructed to place his free arm on his chest and cautioned not to take deep breaths in anticipation of the breath holding. The moment quiet expiration was observed, he was instructed to stop breathing and to cover his nose and mouth with his free hand to prevent the passage of air. The pressure in the cuff was raised to the systolic level and kept there. Exactly at the end of twenty seconds, the systolic reading was taken. The subject was told to breathe normally, and a new basal level was determined. The procedure was then repeated except that this time the diastolic blood pressure was read at the end of the twenty seconds.

In our experiments both tests were explained to the subject at the beginning of the rest period. The breath holding just described was practiced sufficiently to insure exact cooperation.

EXPLANATION OF TERMS

With either test the difference between the basal level and the maximum reading is said to be the range, reaction or response. Subjects

TABLE 1.—*Results of Cold Pressor and Breath-Holding Tests in Two Hundred Subjects*

Group	Cold Pressor Test			Breath-Holding Test		
	Subjects	Mean Rise of Blood Pressure in Millimeters of Mercury		Subjects	Mean Rise of Blood Pressure in Millimeters of Mercury	
		Systolic	Diastolic		Systolic	Diastolic
Normal hyporeactors.....	128	10.91 ± 0.28	12.49 ± 0.34	151	13.23 ± 0.23	12.19 ± 0.30
Normal hyperreactors.....	57	28.09 ± 0.62	24.30 ± 0.55	34	26.85 ± 0.69	21.71 ± 0.64
Hypertensive subjects.....	15	31.93 ± 2.44	20.87 ± 1.96	15	28.47 ± 2.51	21.47 ± 1.69
All subjects combined.....	200	17.38 ± 0.52	16.49 ± 0.40	200	16.73 ± 0.42	14.50 ± 0.34

with normal blood pressure whose reaction did not exceed 20 mm. systolic and 15 mm. diastolic were called normal hyporeactors or normal reactors. Normal hyperreactors were those persons with normal blood pressure who showed a reaction exceeding 20 mm. systolic and 15 mm. diastolic.

SUBJECTS OF TESTS

The cold pressor and breath-holding tests were performed on 185 persons with normal blood pressure and 15 subjects who had elevated blood pressure. All of them were regularly employed in clerical positions. Among the normal subjects there were 137 men and 48 women; the average age of the group was 37.1 years. All of the hypertensive persons were men; the average age was 52 years. The blood pressure was arbitrarily said to be elevated if it was over 145 systolic and/or 95 diastolic after twenty minutes or more of rest in a reclining position. Most of the hypertensive subjects showed blood pressures well above these figures while at rest. No classification was made according to the degree of hypertension, the cause of the hypertension or the secondary cardiovascular-renal changes.

RESULTS OF TESTS

The results are summarized in table 1. Among the 185 subjects with normal blood pressure, 128 (69.2 per cent) gave a hyporeaction to the cold pressor test and showed an average response of 10.91 ± .28 mm.[4] systolic and 12.49 ± .34 mm. diastolic. By comparison, 151 (81.6 per cent) of those with normal blood pressure showed a hyporeaction to the breath-holding test, and the average response was 13.23 ± .23 mm. systolic and 12.19 ± .30 mm. diastolic. There were 57 (30.8 per cent) normal hyperreactors to the cold pressor test; the average rise was 28.09 ± .62 mm. systolic and 24.30 ± .55 mm. diastolic. Thirty-four (18.4 per cent) normal hyperreactors to the breath-holding test showed an average rise of 26.85 ± .69 mm. systolic and 21.71 ± .64 mm. diastolic. Among the subjects with hypertension the average response to the cold pressor test was 31.93 ± 2.44 mm. systolic and 20.87 ± 1.96 mm. diastolic. The average response to breath holding was 28.47 ± 2.51 mm. systolic and 21.47 ± 1.69 mm. diastolic.

COMPARISON OF THE BREATH-HOLDING AND COLD PRESSOR TESTS

The breath-holding test produces a rise in blood pressure, and the cold pressor test produces a rise in blood pressure, but it cannot be said from our results that a "striking similarity" exists in the degree of response. If the arithmetic mean is used in making comparison, the reactions to the two tests do show a remarkable similarity, as seen in table 1. When all 200 subjects, hypertensive persons and those with normal blood pressure, were studied, the mean systolic response to the cold pressor test was 17.38 ± .52 mm. and 16.73 ± .42 mm. to the breath-holding test. The mean diastolic reaction in the 200 persons was 16.49 ± .40 mm. to cold and 14.50 ± .34 to breath holding.

In only one classification was the difference between reactions to the two tests statistically significant.[5] Among normal hyporeactors to the two tests the systolic response to the breath-holding test exceeded the response to the cold pressor by 5.9 times the probable error. It is difficult to evaluate the significance of this difference, and further study will be necessary to determine whether breath holding really produces a greater systolic response in normal hyporeactors.

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4. The figure after the sign is the probable error of the arithmetic mean.

5. Statisticians do not consider a difference between two arithmetic means as "significant" unless it is at least 4 times the probable error in the difference of the two means. The probable error in the difference of two means is equal to the square root of the sum of the squares of the probable errors of the two means. A difference of 4 times the probable error can occur once in 142 times as a matter of chance.

As shown in table 2, individual variations occurred frequently. For example, among normal hyperreactors to the cold pressor test the breath-holding test gave a greater diastolic reaction than the cold pressor test in only 3 (5.3 per cent), while the cold pressor test gave a greater reaction in 41 (71.9 per cent). Among normal hyporeactors to the cold pressor test the breath-holding test gave a greater diastolic reaction in 36 (28.1 per cent), and the cold pressor test gave a greater diastolic reaction in 31 (24.2 per cent). For all 200 subjects the breath-holding reaction was higher in 26.5 per cent systolic and 21.5 per cent diastolic. The cold pressor reaction was higher in 31 per cent systolic and 38.5 per cent diastolic. The cold pressor reaction was the same [6] as the breath-holding reaction in 42.5 per cent systolic and 40 per cent diastolic.

TABLE 2.—*Comparison of Blood Pressure Reactions to Cold Pressor and Breath-Holding Tests*

	All 200 Subjects				128 Normal Hyporeactors to Cold				57 Normal Hyperreactors to Cold				15 Hypertensive Subjects			
Comparison	Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
Reaction to breath holding greater	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	53	26.5	43	21.5	47	36.7	36	28.1	3	5.3	3	5.3	3	20	4	26.7
Reactions to breath holding and cold the same	85	42.5	80	40.0	64	50.0	61	47.7	15	26.3	13	22.8	6	40	6	40.0
Reaction to cold greater	62	31.0	77	38.5	17	13.3	31	24.2	39	68.4	41	71.9	6	40	5	33.3

It is impossible to make a brief tabular analysis of individual differences between the responses to the two tests. Among hypertensive subjects the difference between the response to the cold pressor test and that to the breath-holding test in the same person was at times as great as 20 or 25 mm. Among hyperreactors differences of 10 mm. or more between the responses to the two tests were common.

Although we found 16 hyperreactors to the breath-holding test among 128 normal hyporeactors to the cold pressor test, wide differences were unusual. Of only 4 of the 16 persons could it be said that the cold pressor test gave little or no reaction (diastolic response below 10 mm.). Among 151 normal hyporeactors to the breath-holding test there were 39 who were hyperreactors to the cold pressor test. In 8 of the 39 persons the diastolic response to breath holding was below 10 mm.

6. The responses to the cold pressor and breath-holding tests were considered the same if the difference between them was less than 5 mm.

COMMENT

The foregoing comparison shows that in our series the responses to cold and breath holding were similar when the arithmetic means were compared. The only significant difference in arithmetic means between the two tests was among normal hyporeactors, in whom the breath-holding test gave a greater systolic response. In the entire group the reaction to the cold pressor was the same as or greater than the reaction to the breath-holding test in 73.5 per cent of the systolic readings and 78.5 per cent of the diastolic readings. There were wide individual differences. Ayman and Goldshine stated that some of their subjects showed little or no reaction to the cold pressor but were hyperreactors to the breath-holding test. A few of our subjects showed the same phenomenon, hyperreaction to breath holding but hyporeaction to cold. A much larger number showed just the reverse, hyporeaction to the breath-holding test and hyperreaction to the cold pressor test.

In our experience, with subjects whose intelligence is presumably above average, full cooperation was had for all the breath-holding tests. It is conceivable that this might not always be obtainable. Certainly the test is not adaptable to dyspneic patients, as Ayman and Goldshine pointed out. While the material necessary for a cold pressor test is not always available, this disadvantage is compensated by the fact that a minimum of cooperation is required for its successful completion.

So far we have not been able to confirm all the results obtained by Ayman and Goldshine. We are continuing our studies. Much more evidence will have to be accumulated before it can be said that one test is better than another as a stimulus for measuring blood pressure reactions.

SUMMARY

In the present series of 200 cases the mean responses of the blood pressure to the cold pressor test and the breath-holding test were similar except that breath holding obtained a slightly greater systolic reaction among normal hyporeactors. In most of our subjects the response to the cold pressor test was the same as or higher than the response to the breath-holding test. Wide differences between the reaction to the cold pressor test and the reaction to the breath-holding test were at times found in the same person. Hyperreaction to cold was found in 39 subjects who were hyporeactors to breath holding. Hyperreaction to breath holding was found in 16 subjects who were hyporeactors to cold.

THROMBOSIS OF THE COMMON, INTERNAL AND EXTERNAL CAROTID ARTERIES

A REPORT OF TWO CASES WITH A REVIEW OF THE LITERATURE

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Recently Egas Moniz[1] and Sorgo,[2] after making cerebral arteriographic studies, suggested that thrombosis of the internal carotid artery at its origin is more frequent than is generally supposed. However, unilateral thrombosis of the common and internal carotid arteries without involvement of the subclavian artery and the associated inequality of radial pulses and blood pressures in the two arms is rare. We found reports of only 11 such cases in the literature. Sorgo[2] encountered occlusion of the internal carotid artery in 8 patients and confirmed his diagnosis of this condition in 2 by postmortem examinations. He was able to find 20 more cases by a search of the literature. Thrombosis of the internal carotid artery has been found at autopsy,[3] and Saphir[3c] stressed the importance of searching for obstruction to the internal carotid artery in

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From the Third (New York University) Division of Welfare Hospital for Chronic Diseases.

Read before the Section of Neurology and Psychiatry of the New York Academy of Medicine, Dec. 10, 1940.

1. Egas Moniz; Almeida Lima, and de Lacerda, R.: Hémiplégies par thrombose de la carotide interne, Presse méd. **45**:977, 1937.

2. Sorgo, W.: Ueber den durch Gefässprozesse bedingten Verschluss der Art. carotis interna, Zentralbl. f. Neurochir. **4**:161, 1939.

3. (*a*) Forti, F.: Emplegia per trombose della carotide interna in corso di tifo, Riv. di clin. med. **31**:425, 1930. (*b*) Arteriosclerosis of Internal Carotid Arteries: Cerebral Infarcts, Cabot Case 19471, New England J. Med. **209**:1063, 1933. (*c*) Saphir, O.: Serpentine Aneurysm of the Internal Carotid Artery with Resulting Encephalomalacia and Cerebral Hemorrhage, Arch. Path. **20**:36 (July) 1935. (*d*) Dial, D. L., and Maurer, G. B.: Intracranial Aneurysms: Report of Thirteen Cases, Am. J. Surg. **35**:2, 1937.

the carotid canal and the cavernous sinus (sites which are commonly overlooked at autopsy) in every instance of encephalomalacia and cerebral hemorrhage.[4] Congenital narrowing[5] and, in some instances, absence of one common carotid artery have also been reported.[6]

Hemiplegia due to thrombosis of the common and internal carotid arteries of one side appears to be rare, perhaps, as Hunt[7] suggested, because "these vessels are frequently ignored both in clinical and pathological studies." Recently, 2 patients out of 100 with hemiplegia in the wards of Welfare Hospital for Chronic Diseases were shown to have thrombosis of the carotid arteries of the left side. Both patients had a hyperactive carotid sinus reflex on the side on which the artery was patent.

REPORT OF CASES

CASE 1.—R. S., a 52 year old white man, while at work on July 20, 1938, suddenly lost his ability to speak and to use his arms and legs. He was taken to Morrisania City Hospital, where it was learned from his wife and friends that he had always been healthy except for pneumonia at the age of 30. Observation there revealed spastic hemiplegia of the right side with sensory and motor aphasia, variable arterial pressure (between 210 systolic and 150 diastolic and 180 systolic and 100 diastolic) without cardiac enlargement or renal impairment, and moderate sclerosis of the retinal arteries. The cerebrospinal fluid showed normal dynamics, and its content of sugar and protein and number of cells was normal. The blood and spinal Wassermann reactions were negative. The course of his illness was uneventful.

On July 6, 1939 he was transferred to the neuropsychiatric service of the Third (New York University) Division of Welfare Hospital for Chronic Diseases.

The physical examination on admission gave essentially the same results as at Morrisania City Hospital. In addition, the medical consultant noted a bilateral patchy flush of the skin on the face, neck and upper part of the chest; a mottled livid color of the lower parts of the legs and the arms coexistent with coldness and perspiration, and considerable dermographia. There was moderate sclerosis of the peripheral vessels. Of greatest interest was the absence of pulsation in the left

4. Other sites which should be carefully examined, according to Saphir, are the vertebral arteries and the circle of Willis, particularly for evidence of congenital anomalies.

5. Smith, H. L., and Hinshaw, H. C.: Syncopal Attacks Due to Congenital Anomaly of Right Common Carotid Artery, Am. Heart J. **11**:619, 1936. Elliot, A. H.; Ussher, N. T., and Stone, C. S.: Bilateral Denervation in a Patient Having Syncopal Attacks and Congenital Vascular Anomaly: Unusual Case, ibid. **17**:69, 1939.

6. Boyd, J. D.: Absence of Right Common Carotid Artery, J. Anat. **68**:551, 1934.

7. Hunt, R.: The Role of the Carotid Arteries in the Causation of Vascular Lesions of the Brain, with Remarks on Certain Special Features of the Symptomatology, Am. J. M. Sc. **147**:704, 1914.

internal, external and common carotid and temporal arteries. Bradycardia, sharp fall in arterial pressure and generalized tonic and clonic convulsive seizures occurred on pressure over the right carotid sinus. There was only slight slowing of the pulse on pressure over the left carotid sinus (fig. 1*A* and *B*). Arterial pressure was the same in both arms. The diagnosis was (1) probable thrombosis of the left common, external and internal carotid arteries with right hemiplegia and mixed aphasia, (2) right hyperactive carotid sinus reflex and (3) hypertension, probably of the diencephalic type.

The patient's condition has remained unchanged since admission to Welfare Hospital for Chronic Diseases. An occasional generalized convulsive seizure,

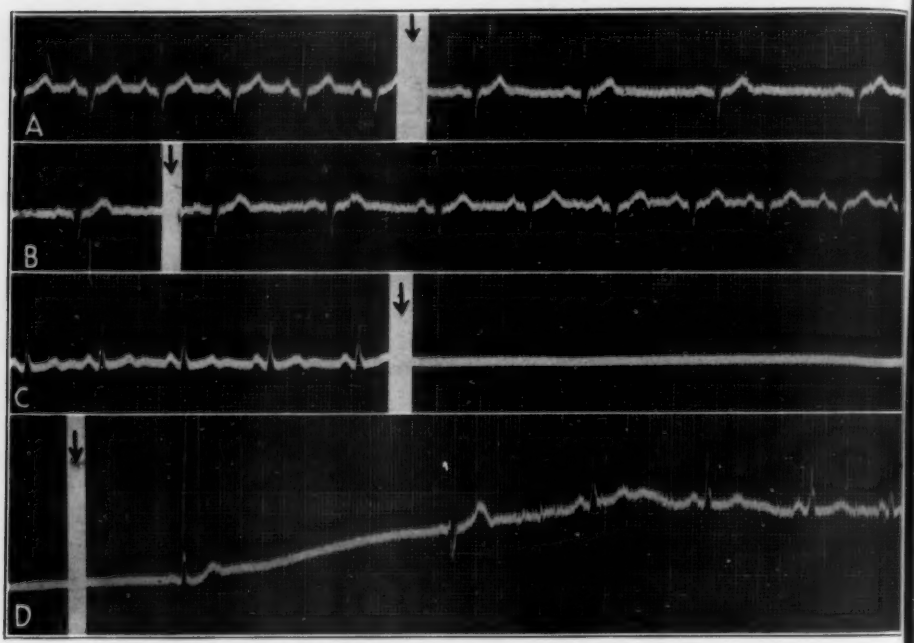

Fig. 1—In *A* (case 1), pressure over the right carotid sinus was begun at arrow and maintained for seven seconds, causing slowing of the heart from 90 to 50 beats a minute. In *B* the arrow indicates release of pressure with gradual return to original rate. In *C* (case 2), pressure over the right carotid sinus was begun at arrow and maintained for six seconds. In *D* the arrow indicates release of pressure, with asystole for six and one-half seconds.

during which he did not lose control of his sphincters or bite his tongue, has occurred. Examination in most instances was made a few minutes after the seizure began and revealed a regular, rapid pulse rate and arterial pressure of 200 systolic and 120 diastolic.

The roentgen shadow of the heart was not enlarged. The aorta was tortuous and sclerotic. The cardiac chambers, visualized by the Robb-Steinberg technic,

were of normal size. The right, but not the left common, carotid artery was visualized (fig. 2).

Roentgenograms of the skull showed a calcified pineal gland, displaced slightly backward. The bony cage was not abnormal. An encephalogram revealed bilateral hydrocephalus with a multilocular cyst involving the anterior half of the left cerebrum and communicating with the left ventricle (fig. 3). A direct injection of 10 cc. of colloidal thorium dioxide into the right common carotid artery (fig. 4) showed that only the vessels of the right cerebral hemisphere could be well visualized. The contrast medium did not pass to the left cerebral hemisphere, even when it was introduced into the exposed right common carotid artery. Electro-

Fig. 2 (case 1).—The contrast substance is visualized in the right common carotid artery (indicated by arrows).

encephalograms, made by Dr. Hans Strauss, showed spontaneous abnormal activity over the left frontomotor region. After stimulation of the carotid sinus there was abnormal activity of an equal degree in both frontomotor regions.

After these preliminary observations, the vessels of the left side of the patient's neck were explored by Dr. W. F. Ruggiero. The common and internal carotid arteries were found to be thrombosed throughout their course in the neck. A needle was inserted into the thoracic part of the common carotid artery for about 5 cm. without obtaining blood, demonstrating that the thrombus extended at least this distance downward. The external carotid artery was thrombosed in

only the first 2 cm.; the lingual and external maxillary arteries were patent and probably furnished part of the collateral circulation. The entire cervical part of the common and internal carotid arteries and the external carotid artery below

Fig. 3 (case 1).—The encephalogram shows bilateral hydrocephalus and a multilocular cyst in the anterior half of the left cerebrum, communicating with the left ventricle.

Fig. 4 (case 1).—In this cerebral arteriogram the right internal carotid artery and the cerebral vessels are visualized. There is no cross circulation to vessels of the opposite hemisphere.

the origin of its lingual branch were removed. Gross and microscopic examination showed thrombosis of these arteries with evidence of arteriosclerosis. The first 1 or 2 cm. of the external carotid artery only and its superior thyroid branch were occluded (fig. 5*A* and *B*).

Laboratory Data.—The urine was normal. The concentration test gave a specific gravity of 1.026. The urea clearance test (Van Slyke) revealed elimination 78 and 76 per cent of normal during two successive hours. The phenolsulfonphthalein test showed 35 per cent excreted during the first hour and 20 per cent during the second hour. An intravenous pyelogram did not show any abnormalities in the urinary tract.

The red blood cells numbered 5,100,000 per cubic millimeter; the hemoglobin was 14.4 Gm. per hundred cubic centimeters. There were 10,200 white blood corpuscles per cubic millimeter, with a normal differential count. Sugar was

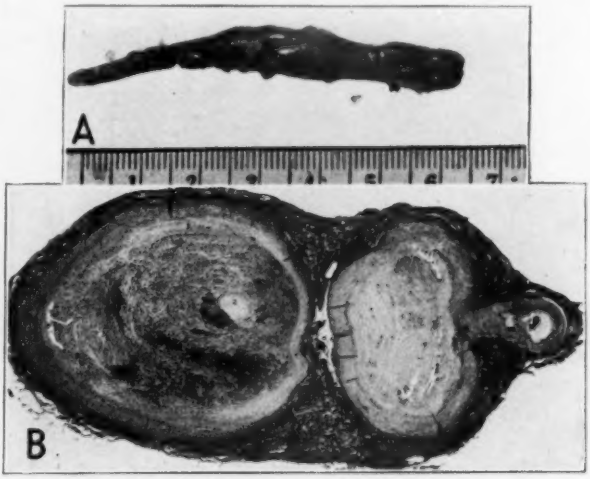

Fig. 5 (case 1).—Cervical portions of the thrombosed common and internal carotid arteries and the first centimeter of the thrombosed external carotid artery and its superior thyroid branch. *B*, photomicrograph of a cross section through the internal carotid artery and the external carotid artery and its superior thyroid branch.

70 mg. per hundred cubic centimeters; urea nitrogen, 12.6 mg.; calcium, 10.6 mg.; phosphorous, 3 mg., and total cholesterol, 207 mg. The total protein was 6.5 Gm., albumin, 4.5 Gm., and globulin, 2.0 Gm., per hundred cubic centimeters. The Kahn and Wassermann reactions of the blood were negative.

The cerebrospinal fluid showed normal dynamics and absence of cells. The result of a qualitative test for sugar was normal, and the Pandy and Wassermann tests were negative. There was 56 mg. of protein per hundred cubic centimeters.

The basal metabolic rate was — 5 per cent.

Case 2.—E. G., a 52 year old white man, on Feb. 21, 1940 was found lying on the street, confused and scarcely able to talk. He was brought by ambulance to Bellevue Hospital.

On admission he was confused and irrational. The arterial pressure was 190 systolic and 110 diastolic; the pulse rate was rapid and regular; the heart was otherwise normal. There were slight weakness of the right arm and leg, absence of abdominal reflexes on the right and absence of knee jerk reflexes on both sides. The ocular fundi exhibited moderate arteriosclerosis. The examinations of the urine, blood and spinal fluid, including the Wassermann tests, gave normal results.

The hospital records show that four years previously (June 25, 1936) he had been admitted to the hospital after a similar occurrence and had been discharged in two days. The diagnosis then had been (1) syncope of unknown cause, (2) essential hypertension and (3) hypertensive and arteriosclerotic heart disease

Fig. 6 (case 2).—In this cerebral arteriogram the right internal carotid artery and a direct communication between the cerebral vessels of both hemispheres are visualized.

with paroxysmal auricular fibrillation. At that time he described his seizures as preceded by dizziness, coughing up of white mucoid sputum and generalized shaking. He did not know how long he remained unconscious and always felt dizzy for one to two days after each seizure. During these attacks he did not lose control of his sphincters or bite his tongue. The seizures began at the age of 34 and occurred as often as six or seven times a month. Occasionally, there would be a free interval of eight or nine months.

On the sixty-fifth day of hospitalization (April 26, 1940), the patient was transferred to the Third (New York University) Medical Division of Welfare Hospital for Chronic Diseases. The diagnosis at that time was (1) left cerebral

thrombosis with right hemiplegia and mixed aphasia, (2) idiopathic epilepsy and (3) generalized and cerebral arteriosclerosis.

On physical examination at Welfare Hospital for Chronic Diseases, additional observations of considerable interest were made. Pulsation of the left common, external and internal carotid arteries was absent. Pulsation of the left temporal artery was present. Light pressure over the right carotid sinus resulted in asystole for a few seconds (fig. 1 *C* and *D*), sharp fall in arterial pressure, loss of consciousness and a generalized tonic and clonic convulsive seizure. Pressure over the left carotid sinus was associated with only slight slowing of the heart rate. There was a defect in the right upper homonymous quadrantic visual field. Pulsations of the vessels of the upper and lower extremities were equal and normal. The radial arteries showed a moderate degree of sclerosis. The arterial pressure was 130 systolic and 70 diastolic in both arms.

The diagnosis was (1) thrombosis of the left common, external and internal carotid arteries with right hemiplegia and mixed aphasia, (2) hypersensitivity of the right carotid sinus and (3) generalized arteriosclerosis.

Fig. 7 (case 2).—This encephalogram shows slight dilatation of the ventricular system, particularly the left lateral ventricle, without displacement. Cortical atrophy is more marked on the left side.

Since admission to this hospital he has not had any spontaneous convulsive seizures, and his general condition has remained unchanged. His arterial pressure has ranged between 210 systolic and 110 diastolic and 130 systolic and 80 diastolic. Roentgenograms showed the chest and heart were normal. The cardiac chambers as visualized by the Robb-Steinberg technic were normal. The vessels of the lower extremities and abdominal portion of the aorta were shown by a roentgenogram to be partially calcified.

A cerebral arteriogram made on May 10, 1940 by an injection of 10 cc. of colloidal thorium dioxide into the right common carotid artery revealed a direct communication between the cerebral vessels of the two hemispheres (fig. 6). This was interpreted by one of us [H. K. T.] as suggestive of occlusion of the left internal carotid artery. The cerebral vessels appeared normal.

An encephalogram made on May 14 indicated slight dilatation of the entire ventricular system, particularly the left lateral ventricle, without displacement, and cortical atrophy, particularly on the left side (fig. 7).

After these observations were made, surgical exploration of the left side of the patient's neck, performed by Dr. W. F. Ruggiero, revealed that the entire

Fig. 8 (case 2).—*A*, cervical portions of the thrombosed common and internal carotid arteries and the first 2 cm. of the external carotid artery. The vessels were opened, and the thrombus pushed to one side, exposing the intimal surface. *B*, photomicrograph of a cross section of the thrombosed common carotid artery just below the carotid bifurcation.

cervical part of the common and internal carotid arteries and the first few centimeters of the external carotid artery were thrombosed. The remainder pulsated feebly. The entire cervical part of the internal and common carotid arteries was removed, and the external carotid artery was sectioned just beyond the carotid bifurcation. A needle was thrust into the thoracic portion of the common carotid artery for a distance of about 5 cm. without obtaining blood, indicating that the thrombus extended at least this distance downward.

Gross and microscopic study of the arteries showed thrombosis of the common, internal and external carotid arteries and arteriosclerotic changes. Only the first centimeter or two of the external carotid artery was occluded (fig. 8).

Laboratory Data.—The urine was normal. The urea clearance test (Van Slyke) revealed elimination 145 per cent of normal in the first hour and 101 per cent of normal in the second hour. The phenolsulfonphthalein test showed excretion of 37 per cent in the first hour and of 8 per cent in the second hour.

The red blood corpuscles numbered 4,920,000 per cubic millimeter; the hemoglobin content was 16 Gm. per hundred cubic centimeters. There were 10,500 white blood corpuscles per cubic millimeter, with a normal differential count. The Kahn and Wassermann reactions of the blood were negative. Urea nitrogen in the blood was 14.7 mg. and sugar 86 mg. per hundred cubic centimeters.

The cerebrospinal fluid showed normal dynamics; the Pandy and Wassermann tests were negative, and the colloidal gold curve was 0000111100. There was 46 mg. of protein per hundred cubic centimeters of spinal fluid, and no cells were seen on microscopic examination.

The basal metabolic rate was — 12 per cent.

COMMENT

Causes of thrombosis of the carotid arteries are not clear since pertinent data and microscopic descriptions of the vessels are frequently omitted in case reports.[8] Sclerosis of the aorta[9] and pressure from an aortic aneurysm appear to be the phenomena most commonly associated with thrombosis of the carotid arteries.[7] Obliterating syphilitic arteritis without aneurysm,[10] embolism[11] and nonsyphilitic arteritis[12] have been reported in a few instances.

8. This paper does not deal with thrombosis following trauma or ligation of these vessels.

9. Poppich, G.: Ueber nicht thrombotischen Verschluss der grossen Gefässostien des Aortenbogens, insbesondere des Ostiums der Carotis communis sinistra, Frankfurt. Ztschr. f. Path. **25**:236, 1921.

10. Darling, S. T., and Clark, H. C.: Arteritis Syphilitica Obliterans, J. M. Research **32**:1, 1915.

11. (*a*) Cohn, B.: Einfache nicht complicirte Embolie der grossern Hirnarterien: A. Der Carotis communis, in Klinik der embolischen Gefässkrankheiten, Berlin, August Hirschwald, 1860, p. 364. (*b*) Fraenkel, E.: Ueber zwei durch totalen Verschluss der linken Carotis complicirte Aneurysmen des Aortenbogens, Virchows Arch. f. path. Anat. **79**:509, 1880. (*c*) Eichhorst, H.: Ueber Emboli der Carotis communis, Med. Klin. **32**:885, 1907. (*d*) Haffner, S.: Obliteration der Carotis communis sinistra und beider Arteriae brachialis in Folge von embolischer Arteritis bei Herzfehler, Deutsches Arch. f. klin. Med. **60**:523, 1898.

12. Harbitz, F.: Bilateral Carotid Arteritis, Arch. Path. **1**:499 (April) 1926.

Sclerosis of the carotid arteries seems to be not uncommon even in young adults.[13] Egas Moniz [1] and Sorgo [2] have suggested the presence of severe sclerosis of the carotid arteries in some patients to account for obscure neurologic symptoms. Keele [13b] studied the pathologic changes in the carotid vessels and compared them with the alterations in the aortic arch and in the iliac and innominate arteries in 55 successive unselected cases in which postmortem examinations were made. The ages ranged from 7 to 79 years. The carotid sinuses of 50 of the 55 patients showed sclerotic changes. Thirty-two of these, whose average age was 45 (ranging from 16 to 79 years), had slight to extreme fatty flecking of the carotid sinus; the remaining 18 patients, whose average age was 62 years (ranging from 42 to 76 years), had slight to extreme calcification. The lower part of the carotid sinus was more frequently affected than the upper. The common carotid artery was less frequently sclerotic than the carotid sinus, and the most noticeable changes occurred just below the point of bifurcation. The angle of bifurcation also was commonly affected. Sclerosis of the external carotid artery rarely occurred and then only at the points of origin of the branches. The internal carotid artery was not involved to the "slightest degree" in any of the cases. (Keele's observations appear to have been restricted to the cervical part of the internal carotid artery.) The same degree of sclerosis was usually present in the aortic arch and in the innominate and common iliac bifurcation as in the carotid sinus and the upper end of the common carotid artery. It is apparent that sclerosis of the vessels of the neck is part of a generalized process. Dow [14] and Saphir [3c] have shown that appreciable sclerotic change in the internal carotid artery in its course through the carotid canal and cavernous sinus is not infrequent.

The effect of ligation of the great vessels of the neck has been studied clinically and experimentally.[15] It has been stated that unilateral ligation or spontaneous occlusion of the common carotid artery is followed in 10 to 30 per cent of the cases by cerebral damage. In spite of

13. (*a*) Beneke, R.: Die Atherosklerose der Carotis communis und ihre Bedeutung für das Verständnis der Blutsäulenformen, Frankfurt. Ztschr. f. Path. **28**:407, 1922. (*b*) Keele, C. A.: Pathological Changes in the Carotid Sinus and Their Relation to Hypertension, Quart. J. Med. **2**:213, 1933.

14. Dow, R. D.: The Incidence of Arteriosclerosis in the Arteries of the Body, Brit. M. J. **2**:162, 1925.

15. (*a*) Dorrence, G. M.: Ligation of the Great Vessels of the Neck, Ann. Surg. **99**:721, 1934. (*b*) Pilcher, C., and Thuss, C.: Cerebral Blood Flow, Arch. Surg. **29**:1024 (Dec.) 1934. (*c*) Wortis, H.: A Case of Cerebral Degeneration with Encephalographic Study Eight Years After Common Carotid Ligation, Am. J. M. Sc. **192**:517, 1936. (*d*) Shipley, A. M.; Winslow, N., and Walker, W. W.: Aneurysm in the Cervical Portion of the Internal Carotid Artery: An Analytical Study of the Cases Recorded in the Literature Between August 1, 1925 and July 31, 1936, Ann. Surg. **105**:673, 1937.

the rich network of anastomoses between large cerebral arteries and the "endless continuous net" of cerebral capillaries, it is surprising that occlusion of one or even both common carotid arteries is not necessarily followed by cerebral symptoms.[15a] Hunt[7] expressed the opinion that in most instances, "especially in young subjects with good hearts and elastic vessels," the collateral circulation through the circle of Willis is sufficient. More recently, however, Pilcher and Thuss[15b] were unable to find a correlation between the age of the subject, cerebral arteriosclerosis and cerebral complications following occlusion of the common carotid artery.

The evidences of spontaneous occlusion of one common carotid artery are various. As has been mentioned, clinical manifestations may be absent.[10] Diminution of vision in the homolateral eye,[16] unilateral headache,[17] vertigo,[18] epileptiform[19] and convulsive seizures[20] and mental deterioration have been described in the absence of neurologic signs. Hemiplegia is common and may be transient at its onset or may increase gradually, with or without sensory disturbance or aphasia.[21] And yet

16. (*a*) Penzoldt, F.: Ueber Thrombose (autochthone oder embolische) der Carotis, Deutsches Arch. f. klin. Med. **28**:80, 1881. (*b*) Baumler: Thrombotischer Hemiplegie infolge vom Verschluss der linken Karotis, München. med. Wchnschr. **54**:2500, 1907. (*c*) Raeder, J. G.: Ein Fall von symmetrischer Karotisaffection mit präseniler Katarakt und "Glaukom" sowie Gesichtsatrophie, Klin. Monatsbl. f. Augenh. **78** (supp.):63, 1927. (*d*) Marinesco, G., and Kreindler, A.: Oblitération progressive et complète des deux carotides primitives, Presse méd. **44**:833, 1936. (*e*) Egas Moniz, Almeida Lima and de Lacerda.[1] (*f*) Hunt.[7] (*g*) Harbitz.[12]

17. Egas Moniz, Almeida Lima and de Lacerda.[1] Sorgo.[2] Hunt.[7] Marinesco and Kreindler.[16d]

18. (*a*) Crawford, J. R.: Bilateral Pulse Obliteration in Thoracic Aneurysm, J.A.M.A. **76**:1395 (May 21) 1921. (*b*) Kampmeier, R. H., and Neumann, V. F.: Bilateral Absence of Pulse in the Arms and Neck in Aortic Aneurysm, Arch. Int. Med. **45**:513 (April) 1930.

19. Penzoldt.[16a] Marinesco and Kreindler.[16d]

20. Sorgo.[2] Harbitz.[12] Marinesco and Kreindler.[16d]

21. (*a*) Savory, W. S.: Case of a Young Woman in Whom the Main Arteries of Both Upper Extremities and Left Side of the Neck Were Throughout Completely Obliterated, Med.-Chir. Tr. **39**:205, 1856. (*b*) Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1894, p. 517. (*c*) Erb, W.: Ein Fall von ausgedehnter Gehirnerweichung bei totaler Obliteration der Carotis communis sinistra, München. med. Wchnschr. **51**:946, 1904. (*d*) Chao, W. H.; Kwan, S. T.; Lyman, R. S., and Loucks, H. H.: Thrombosis of the Left Internal Carotid Artery, Arch. Surg. **37**:100 (July) 1938. (*e*) Egas Moniz, Almeida Lima and de Lacerda.[1] (*f*) Sorgo.[2] (*g*) Cohn.[11a] (*h*) Haffner.[11d] (*i*) Penzoldt.[16a] (*j*) Hunt.[7]

obstruction of both common carotid arteries may occur with no more striking symptoms than dizziness and occasional syncope.[22]

The association of sensitivity of the carotid sinus and thrombosis of the carotid artery in these 2 patients is interesting. It is well known that the carotid sinus in arteriosclerotic persons is frequently sensitive to light external pressure and that a sensitive carotid sinus may be present without the person's ever having had episodes of syncope or related manifestations.

The history of one of our patients (case 2) strongly suggested that he had suffered from attacks of carotid sinus syncope since the age of 34. In both patients sensitivity of the carotid sinus was accompanied by a sharp fall in systolic and diastolic arterial pressure, marked slowing of the heart rate and generalized convulsive seizures.

In these 2 cases sensitivity of the carotid sinus and arteriosclerosis may have been mutually conducive to thrombus formation. Pronounced slowing of the blood stream for several seconds at a time together with irregularity and roughening of the intima of the internal and common carotid arteries would seem to present conditions generally recognized as conducive for thrombus formation.

Mention of examination for sensitivity of the carotid sinus was found in only 2 cases of carotid artery thrombosis. In one that of a person who suffered from "epileptiform seizures," unilateral stimulation of a carotid sinus was accompanied by convulsive seizures with little change in the arterial pressure and pulse rate.[18b] Tests were made on only one carotid sinus, the other having been removed. In the other [16b] there was only minimal response to stimulation of the thrombosed sinus; there was none to stimulation of the contralateral sinus.

It is interesting that in both our cases pulsations of the common, internal and external carotid arteries were not felt, and only in the second the patient (case 2) did the temporal artery of the thrombosed side pulsate. At operation we saw that both the common and internal carotid artery were thrombosed but that only the first 2 cm. of the external carotid artery was thrombosed. The remainder of the vessel pulsated freely but feebly and apparently received blood from collateral vessels.

22. Yelloly, J.: Case of Preternatural Growth in the Lining Membrane Covering the Trunks of the Vessels Proceeding from the Arch of the Aorta, Med.-Clin. Tr. **12**:565, 1823. Broadbent, W. H.: Absence of Pulsation in Both Radial Arteries, the Vessels Being Full of Blood, Tr. Clin. Soc., London **8**:165, 1875. Shikhare, P. V.: Notes on the Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, Indian J. Med. **2**:526, 1921. Cooley, L. E., and McNamara, F. P.: Syphilitic Aortitis with Aneurism of the Innominate Artery and Occlusion of the Left Common Carotid Artery, Am. Heart J. **9**:686, 1933. Cohen, H., and Davie, T. B.: Bilateral Obliteration of Radial and Carotid Pulses in Aortic Aneurysm, Lancet **1**:852, 1933. Mauer, E.: Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysm of the Aortic Arch, Am. Heart J. **17**:716, 1939. Crawford.[18a] Kampmeier and Neumann.[18b]

*Data on Twelve Cases of Thrombosis of the Carotid Arteries Without Obstruction of the Subclavian Artery**

Authority and Date		Age of Patient, Years	Sex	Cause	Location of Carotid Thrombus	Condition of Cerebral Arteries	Condition of Brain	Comment
Davy, 1845, cited by Chevers, N.: Effects of Obliteration of the Carotid Arteries on the Cerebral Circulation, London M. Gaz. **36**: 1146, 1845		Middle age	♂	?	Left	Injected and dilated mostly on left side	Softening on left	Sudden right hemiplegia 6 weeks prior to death; dilated aortic arch
Cohn,[11a] 1860		66	♂	Embolus ?	Left	Thrombosis of middle cerebral artery	Softening on left	Hemiplegia; recovery; stroke and return of hemiplegia 6 months later, with death in 5 days
Fraenkel,[11b] 1880	Case 1	50	♂	Aortic aneurysm	Left	Thrombosis of middle cerebral artery	Large softening on left	Right hemiplegia; aphasia; later oculomotor paralysis; death in 3 months
	Case 2	54	♂	Aortic aneurysm	Left	Cerebral vessels not referred to	Softening on left	Transient aphasia; hemiplegia; progressive mental impairment; twitchings of face and extremities
Penzoldt,[10a] 1881	Case 1	50	♂	?	Right (artery apparently arose directly from aortic arch)	Thrombosis of middle cerebral artery	Large softening on right	Sudden diminution of vision; later left hemiplegia and hemianesthesia, and epileptiform seizures; death after 1 year
	Case 2	43	♂	?	Left	Thrombosis of middle cerebral artery	Softening on left	Mental disturbances for 1 year; sudden collapse; death after 2 years
Oppenheim* [21b] 1804		?	?	Obliterating arteritis	Cervical portion (?), side	?	Softening	Hemiplegia developed slowly
Erb,[21c] 1904		50	♂	Aortic aneurysm	Left	Thrombosis of middle and anterior cerebral arteries	Large cyst with porencephaly	Aneurysm; pulseless left common carotid artery; hemiplegia and aphasia for 4 years
Eichhorst,[11c] 1907		49	♀	Embolus	Left	Left internal carotid and proximal part of sylvian branches occluded	No softening; less blood on left side	Sudden onset of "cerebral apoplexy"; right hemiplegia 4 days prior to death; history of "acute endocarditis" with embolic phenomena
Darling and Clark,[10] 1915	Case 2	34	♂	Syphilitic arteritis	Left (right carotid and right subclavian arteries arose from aorta separately)	Not recorded	Left side slightly smaller	Died of malaria; Wassermann test positive; no cerebral symptoms
	Case 3	23	♀	Syphilitic arteritis	Left (arose from innominate artery)	Not recorded	Cyst on left	Died of streptococcic infection; Wassermann test positive; no cerebral symptoms
Gladston, Govons, Wortis and others, 1940	Case 1	52	♂	Arteriosclerosis	Left	No cross circulation seen in cerebral arteriogram	Marked cystic changes on left	Sudden right hemiplegia, 2 years; hypertension of "diencephalic type"; hypersensitivity of right carotid sinus
	Case 2	54	♂	Arteriosclerosis	Left	Cross circulation seen in cerebral arteriogram	Hydrocephalus on left	Convulsions since 24 years of age; right hemiplegia, 1 year; moderate arterial hypertension; sensitivity of right carotid sinus

* Oppenheim referred to 2 similar cases reported by Trenel and E. Brissaud and de Massary (L'hémiplégie progressive, Rev. Neurol. **6**: 579, 1898). He gave only the reference to the work of the latter two. They reported slowly developing right hemiplegia in a 49 year old man. Postmortem examination revealed "annular end- the left rolandic area was soft and edematous. arteritis" of the carotid artery without thrombosis. The inferior two thirds of

Review of the literature (table) brings to light the interesting fact that in 9 of the 11 cases reported, thrombosis of the common and internal carotid arteries occurred on the left side.[23] This was also true in our 2 cases. In the single case in which thrombosis of the common and internal carotid arteries occurred on the right side, it was associated with a vascular anomaly. In 5 of the 11 patients the occlusions were caused by vascular syphilis; in 2 by embolism; in 1, by obliterating arteritis, and in 3 the cause was not discovered. Our 2 cases are the only ones that have been reported in which there was associated sclerosis of these arteries. Explanation of the predominant sinistral incidence of this condition is far from clear. It is known that there is a greater variation as regards the site of origin of the left common carotid artery than the right common carotid artery.[24] However, developmental anomalies were not relevant in any of the cases. Eight of the 11 patients were men; both our patients were men. The ages varied from 23 to 66, with an average of 47 years; our 2 patients were 52 and 54 years of age.

SUMMARY

The case histories of 2 patients with right hemiplegia and mixed aphasia associated with thrombosis of the carotid arteries of the left side and sensitivity of the carotid sinus reflex of the other side are presented. The literature dealing with thrombosis of the carotid arteries is summarized.

Thrombosis of the carotid vessels was suspected because of the absence of arterial pulsations. The diagnosis was confirmed by study of cerebral arteriograms and encephalograms, surgical exploration and gross and microscopic examination of the specimens.

Careful examination of the arteries of the neck in all patients with hemiplegia, convulsive seizures or syncope may lead to more frequent diagnosis of thrombosis of the carotid arteries. Often arteriography can be a diagnostic aid.

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23. In 1 instance the author failed to mention the side involved, the age or the sex of the patient.

24. Cunningham, D. J.: Textbook of Anatomy, ed. 7, London, Oxford University Press, 1937, p. 1166.

Progress in Internal Medicine

BLOOD

REVIEW OF RECENT LITERATURE

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A special effort has been made to consider all of the articles which contribute new information related to the blood and the blood-forming organs. Many of the contributions supplement or confirm present concepts; others offer explanations of certain phenomena which are known to exist. In a review of this nature, in which the available material is so correlated as to be of interest to the reader, many articles may appear unduly stressed, while others of equal merit seem to be overlooked. It is significant to point out also that the number of published articles this year is considerably less, and many of the foreign ones could not be obtained. It is hoped that the omissions which have occurred for one reason or another may be corrected in succeeding reviews.

PERNICIOUS ANEMIA

During the past year, the largest number of articles concerned with this disease have dealt either directly or indirectly with Castle's theory concerning the cause of the anemia of pernicious anemia, which was first elucidated by him in 1929. His interpretation of the role played by the stomach has been subjected to minor criticisms, but in the main it has been sustained. In three papers gastroscopic observations on the mucosa of the stomach are reported. There are several general résumés of knowledge concerning the effect of total gastrectomy in animals in relation to the exhaustion of the erythrocyte-maturing factor in the liver and the production of macrocytic anemia. The puzzling question of the cause of changes in the nervous system still remains unsolved, although some interesting possibilities which have a bearing on etiologic factors have been presented during the past year. Two of the most

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important papers deal with the demonstrated observation that changes in the cord will not progress provided the patient is adequately treated and with a determination of the time interval before evidence of the disease will recur after treatment is discontinued. Several papers have appeared which confirm the belief, expressed some years ago, that pernicious anemia is a hereditary disease.

Etiology.—Heredity: Stamos [1] reviews the previous studies dealing with the role of heredity in pernicious anemia and analyzes the hereditary incidence of anemia among over 600 patients studied at the Simpson Memorial Institute of the University of Michigan. According to the author, there is an increasing tendency in the more recent literature to regard the hereditary influence in pernicious anemia as an important factor in the pathogenesis of the disease. In any study of the familial incidence a number of difficulties confront the observer: (1) errors in diagnosis; (2) difficulty in studying all members of a family, due to their residence in different parts of the country; (3) failure to recognize pernicious anemia as a cause of death in some families; (4) death from accident or incidental disease early in life of members of families, which may affect the statistics, and (5) the possibility that the disease may develop later, even though a member of a family may be in perfect health at the time the study is made, since pernicious anemia tends to occur in the later decades of life. In a study of 645 unselected authenticated cases of pernicious anemia, Stamos found evidence of 51 instances in which there were 1 or more cases in the same family, a familial incidence of 7.9 per cent. In 34 of the 51 families, 1 member other than the patient was found to have the disease, the mother, being affected in 10 instances, the father in 8, the sister in 11 and the brother in 5. Two family histories revealed the presence of pernicious anemia in an uncle and in a paternal aunt, respectively. Five families were represented in which 3 or more of the immediate children had the disease. It is of interest that in a large group of patients with pernicious anemia about 27 per cent stated that there was another case of "anemia" in the family. In a control group of patients without pernicious anemia only 9 per cent made this statement. Stamos believes that the results of this study suggest the importance of a familial hereditary factor in the disease.

Schemm [2] reports that in 32 cases of pernicious anemia he observed a familial incidence of 18.7 per cent. However, he regards the true familial incidence as higher. Five authenticated cases, those of 4

1. Stamos, H. F.: Heredity in Pernicious Anemia, Am. J. M. Sc. **200**:586, 1940.

2. Schemm, F. R.: Pernicious Anemia Family: Five Authenticated Cases in Same Generation, Am. J. M. Sc. **199**:167, 1940.

brothers and 1 sister, occurring in one family are reported. One additional sister remains in good health, and the only other living member of the family cannot be persuaded to submit to an examination. Two other cases are reported in each of 5 families. Some of the difficulties of studying the hereditary aspect of pernicious anemia are emphasized. For example, it required Schemm five years to accumulate these data, as the patients resided in widely separated points (Philadelphia to Los Angeles).

Askey [3] has made a study of cases of "potential" pernicious anemia and suggests a plan of study whereby the disease may be recognized in the latent stage. He considers that the incidence in certain families is such that the genetic factor cannot be questioned. Two hundred and thirty-five instances of multiple familial occurrences were found in the literature, and the disease has been reported in 8 pairs of identical twins; in 4 pairs it appeared in both members, and in 3 it was probably latent in the second member. In the remaining pair, aged 86, although both members had anemia, the second had free acid in the gastric secretions. Furthermore, it has been shown that achlorhydria has an increased incidence in the families of patients with pernicious anemia; reports of many cases have now been collected which indicate that the anacidity precedes the development of the active signs of the disease by many years. Askey considers that persons most likely to have pernicious anemia are those relatives of a patient known to have the disease who show a histamine-refractory anacidity. Bloomfield states that the occurrence of anacidity in a person who has no relative with the disease represents a negligible hazard as regards the risk of later development of pernicious anemia, and he estimates the possibility as 1:300 or 400. There are no data available as a basis for estimating the extra hazard of achlorhydria in relatives of patients with pernicious anemia. Askey studied 20 families in which 2 or more members had pernicious anemia, which makes a total of 235 such families recorded in the literature. This incidence and the occurrence of the disease in monozygotic twins suggest that the disease is frequently, if not invariably, transmitted by heredity. He finds anacidity is twice as high in near relatives as in distant ones. Of the 61 relatives examined, 10, or 16 per cent, were found to have achlorhydria and 4 were considered to have incipient pernicious anemia, as evidenced by macrocytic anemia in 3 and a clearcut history of glossitis and paresthesia relieved by liver therapy in the fourth. Two other relatives had hypochromic anemia. In 2 of the relatives who refused to have a gastric analysis and treatment pernicious anemia subsequently developed, with severe changes in the spinal cord.

3. Askey, J. M.: Prevention of Pernicious Anemia: Recognition of Latent Stage in Relatives, Ann. Int. Med. **14**:593, 1940.

Askey considers that the development of pernicious anemia and the neurologic complications can be prevented in many instances if all relatives with anacidity are considered as potentially having the disease.

The diagnosis of pernicious anemia in a child is one to arouse suspicion, and Templeton [4] emphasizes that the disease is rarely encountered in persons younger than 20 years of age. He reports the case of a girl aged 14 and ventures the opinion that she had been suffering from the condition for at least three years. All her life she apparently had been on a deficient diet, especially with respect to protein. According to the author, she "never ate a square meal." Nausea at the sight of most meals was followed by a loose stool and a feeling of distress. For three years there had been periods of moderate pyrexia and extreme weakness. For about a year she had suffered from deep, painful and punched-out buccal ulcers on the tongue, cheeks and lips, and the tongue had begun to appear beefy. A blood count at the time of the latter change showed "a secondary anaemia," with a color index less than 1. About six months later, for the first time, the color index was about 1. The red blood cell count was 2,040,000 per cubic millimeter, the hemoglobin concentration 47 per cent, the white blood cell count 6,400 per cubic millimeter and the color index 1.1. Macrocytosis, microcytosis, poikilocytosis and polychromasia were noted. A fractional test meal showed complete achlorhydria. Full doses of an extract of fresh liver (campolon) and iron had no effect, but 2 cc. of purified liver extract (anahaemin) every other day produced a beneficial effect, and in about three months the blood was entirely normal. In our opinion, this patient may have had true addisonian anemia, but it is difficult to prove from the information which is presented. There is no statement that the patient had achlorhydria after injection of histamine; no data are given about the size of the cells as indicated by the mean corpuscular volume; no neurologic manifestations are mentioned; no data are presented concerning the presence or absence of a reticulocyte response immediately following treatment, and there is nothing to indicate that her condition would not have remained normal if a well balanced diet had been given and the liver extract discontinued. It is impractical, but possible, to ascertain the presence or absence of the so-called intrinsic factor in patients with questionable pernicious anemia. It was not done in this case. The burden of proof is on the one who claims that a child of 14 has pernicious anemia, which means that the diagnosis must be established by all possible means before it can be accepted. A follow-up note on this patient after an interval of several years would be of interest.

Role of the Stomach and the Liver in the Causation of Pernicious Anemia: Since Castle's original hypothesis regarding the formation

4. Templeton, W. L.: Pernicious Anaemia in Child, Lancet **2**:1221, 1939.

of the erythrocyte-maturing factor was evolved in 1929, new information has come to light, and in the opinion of Formijne [5] a reconsideration of all available data has become necessary. He has carried out a number of experimental studies which have a bearing on the cause of pernicious anemia and on the mechanism of the normal control of the formation of erythrocytes. The following results were obtained by the author in regard to the extrinsic factor. It was present in a 70 to 80 per cent alcoholic extract of meat; fats and lipoids could be removed from this extract by ether extraction without loss of activity and the extrinsic factor present in the extract passed through an ultrafilter. Less than 50 per cent of the extrinsic factor was present in the precipitate obtained by saturation of the extract with ammonium sulfate. In studying the interaction between the extrinsic and the intrinsic factor in vitro, the author concluded:

> The liver factor [erythrocyte-maturing factor] could not be demonstrated by treatment of the incubated mixture with 70 per cent alcohol and precipitation of the filtrate with 96 per cent alcohol; the precipitate was inactive when given by mouth or by injection.

The conclusion is drawn, contrary to the belief expressed by Wilkinson and his collaborators, that no reaction occurs between the extrinsic and the intrinsic factor in vitro and that only an in vivo reaction exists.

Geiger, Goodman and Claiborn [6] state that there are no observations which either have proved a simple storage function of the liver as regards the antianemia, erythrocyte-maturing factor or have excluded the possibility that the active principle is produced by an essential function of the normal liver tissue. In order to test the theory of liver storage of the antianemia principle, stomachs were removed from swine and it was then determined whether the livers of these animals showed a progressive depletion of the effective factor. Totally gastrectomized animals were killed at approximately monthly intervals between the second and the sixth month after operation and also at eighteen and thirty-six months. The livers from these animals were then assayed for the anti-pernicious-anemia principle by administration to patients with pernicious anemia of an extract prepared from them. From the results of these experiments, it is clear that after total gastrectomy in the hog the liver becomes progressively depleted of antianemia potency. An appreciable loss is apparent after the second postoperative month, and the exhaustion is complete after the sixth month. These results con-

5. Formijne, P.: Experiments on the Properties of the Extrinsic Factor and on the Reaction of Castle, Arch. Int. Med. **66**:1191 (Dec.) 1940.

6. Geiger, L. S.; Goodman, L. S., and Claiborn, L. N.: Effects of Gastro-Intestinal Resections in Swine on Antianemia Potency of Liver: Observations on Nature and Sources of Materials Effective in Pernicious Anemia, Yale J. Biol. & Med. **13**:259, 1940.

firm previous reports by these and other authors and suggest strongly that the liver serves merely to store, or to elaborate and store, a product furnished by the stomach. They throw no light on whether the erythrocyte-maturing factor is an interaction product of gastric digestion, a precursor which is further elaborated by the liver cells into the antianemia principle or a hormone originating in the stomach wall. A second series of experiments was designed to determine whether the antianemia principle is a hormone or a product of gastric digestion. One part of this question was answered by an ingenious experiment in which the continuity of the stomach with the gastrointestinal tract in swine was severed completely at both the cardiac and the pyloric end, while as much as possible of the gastric nerve and blood supply was preserved. Under such conditions, according to the theory of Castle, the interaction between the extrinsic food factor and the intrinsic gastric factor would be disturbed and the liver would suffer loss of potency, precisely as after gastrectomy. The animal on which such an operative procedure had been carried out was killed in the eighth postoperative month. Assay of this liver on 2 patients with pernicious anemia indicated that it did not contain the anti-pernicious-anemia principle. It appears, therefore, that the digestive role of the stomach is essential to the formation of the erythrocyte-maturing factor present in liver. Results of further experiments indicated that the liver of the newborn pig has some reticulocytogenic effect, although apparently less than is found in normal adult hog liver, and that the livers of fetuses obtained from an agastric sow are lacking in this principle. These observations tend to corroborate those on the isolated stomach preparation, and the two together imply that gastric digestion is essential for the production of the antianemia principle. Another experiment was done to determine if the duodenum of the hog was a significant source of the anti-pernicious-anemia factor. The proximal 15 feet (457 cm.) of intestine was removed from a hog and the stomach left intact. The animal was killed eight months later. Assay of the liver from this animal showed an appreciable decrease in the antianemia principle. Thus it appears that the duodenum is a true and significant source of the intrinsic factor, but that it is relatively less important than the stomach in this respect.

An attempt was made to produce pernicious anemia in swine by extirpating all known sources of the intrinsic factor, namely, the stomach and the duodenum. In 2 pigs the entire stomach and 15 to 20 feet (457 to 609 cm.) of the proximal portion of the intestinal tract was removed. Assays of the livers of the 2 animals at the end of six weeks and four months, respectively, showed that extirpation of both the stomach and the duodenum exhausts the liver of antianemia principle more quickly than does the removal of either organ alone. Observations

on changes in the bone marrow, the blood and the nervous system are to be published at a later date. The authors conclude from these experiments that the liver stores, or elaborates and stores, a product furnished by the stomach. As the liver is depleted in the isolated stomach preparation, it is suggested that the effective factor results from gastric digestion rather than from an internal secretion of the stomach. The fact that livers of newborn pigs from a normal sow contain the active principle and that the livers of the newborn pigs from an agastric sow do not also suggests that the active factor is a product of gastric digestion. Results of additional experiments indicate that the duodenum, as well as the stomach, is a true source of the intrinsic factor. Because these authors have contributed new and important information bearing on the cause of pernicious anemia, their paper deserves the careful perusal of all those who are interested in the disease.

Relation of Gastrectomy to Pernicious Anemia: It is considered by Ivy [7] that the functions of the stomach are those of (1) a reservoir and (2) of a triturating, (3) digestive, (4) hematopoietic, (5) bacteriostatic and bactericidal and (6) coabsorptive organ. He believes that observations on gastrectomized animals indicate that the stomach cannot be considered as an essential organ in a strict sense. Since 1923 attempts have been made in Ivy's laboratory to produce the blood and bone marrow picture of pernicious anemia in animals by gastrectomy and dietary modification. All attempts have met with failure, and the author has no faith in the few reports to the contrary which appear in the literature. He believes that the differences observed between the reaction to gastrectomy of the rat and the pig, on the one hand, and that of the dog and the monkey, on the other, in regard to anemia may be due to a true "species difference." He suspects, however, that the difference is more likely attributable to "the degree of success that has been attained in the search for an adequate diet" following gastrectomy. With the diet he has employed after gastrectomy changes have not occurred in the mouth, tongue, skin or nervous system. An important point is stressed, as follows:

> Obviously the presence of diarrhea or mushy stools, especially if associated with rapid intestinal passage, will predispose to mineral, vitamin and protein loss, all of which are concerned in the genesis of the various disturbances observed in gastrectomized animals.

It is concluded that total gastrectomy does not cause pernicious anemia, combined degeneration of the spinal cord, stomatitis and glossitis in the rat (after one year), dog (after twelve years), pig (after three years) or monkey (after two and six-tenths years).

7. Ivy, A. C.: Effects of Gastrectomy in Animals, Am. J. Digest. Dis. **7**:500, 1940.

Bussabarger, Ivy, Wigodsky and Gunn [8] were led to investigate the effects of gastrectomy in the monkey because they realized that until pernicious anemia can be produced experimentally its cause will probably remain uncertain. From Castle's studies they concluded that the complete removal of the stomach from animals should provide valuable corroborative data relating to his hypothesis. After observations on the blood of 8 monkeys were recorded for one month under normal conditions, the stomach was removed and the lower end of the esophagus anastomosed to the duodenum. Two of the animals succumbed within a period of three weeks after the operation. One died of tuberculosis one hundred and eighty-seven days after the operation. The remaining 5 survived four hundred and seventy-eight to nine hundred and thirty-seven days, and they would have lived longer if it had not been for certain experiments. In none of them did there develop the blood picture of pernicious anemia as seen in man. This work confirms that of Goldhamer, who reported that gastrectomy in the monkey is followed after six months not by the blood picture of pernicious anemia but by that of anemia with a low color index. These observers can say further that such a blood picture did not appear within approximately three years. Sometimes the hypochromic anemia which was observed responded to the administration of ferric citrate and liver extract, but at other times it did not. In some instances it disappeared spontaneously. One monkey, whose pregnancy was first diagnosed seven hundred and sixteen days after gastrectomy, delivered a full time fetus. Although this animal did not have anemia during pregnancy, the condition occurred during the puerperium, with a red blood cell count as low as 3,740,000 per cubic millimeter. Two gastrectomized monkeys and 1 normal animal were fed a diet devised by Wills, similar to that of Mohammedan women in Bombay, who frequently have macrocytic anemia. None of the animals survived on this diet more than one hundred and fifty-two days, but at the time of death none had macrocytic anemia. The bone marrow of a gastrectomized monkey fed such a diet showed a great proliferation of undifferentiated cells (hemocytoblasts) and an excessive quantity of pigment. These changes were not reflected in the circulating blood. A comprehensive discussion of the cause of pernicious anemia, with especial reference to the gastric factor, is presented, and a complete bibliography is given.

The establishment of the fact that the stomach secretes the intrinsic factor which is concerned with the development of the red blood cells and with the causation of pernicious anemia makes gastrectomy, complete or partial, a procedure which must be considered from these

8. Bussabarger, R. A.; Ivy, A. C.; Wigodsky, H. S., and Gunn, F. D.: Effect of Gastrectomy on Monkey, Ann. Int. Med. **13**:1028, 1939.

standpoints, according to Jones.[9] A careful review is given of the investigations dealing with the relation of the stomach to the anemias and with the effects of gastrectomy. The author concluded that a major gastric operation, such as either total or subtotal gastrectomy, may be performed without any great concern or undue consequence as far as interference with normal hematopoiesis is concerned. Regardless of the fact that relative or absolute achlorhydria may result and the secretory cells of importance to normal physiologic activities of the blood may be removed, the development of serious anemia need not be feared. It is admitted that occasionally severe microcytic or macrocytic anemia may follow an extensive operation on the stomach, but in all probability it can be readily controlled with iron and/or liver therapy. The author concludes with this statement:

> The search for the exact site of formation of the intrinsic antianemic factor must still be pursued, but in spite of our lack of accurate knowledge as to its source, proper gastric surgery need not be avoided.

Gastroscopic Observations in Patients with Pernicious Anemia: According to Schindler and associates,[10] atrophic gastritis is found constantly in cases of pernicious anemia, sprue and combined degeneration of the cord and in many cases of gastric carcinoma, in which it apparently precedes the development of the tumor. It is also claimed that atrophic gastritis, without associated disease, may occur. This appears to be a primary disease entity of unknown etiology. A number of investigators have observed that the gastric mucosa will regenerate completely after liver therapy in cases of atrophic gastritis associated with pernicious anemia. It has also been noted by others, and confirmed, that a similar regeneration of atrophic mucosa will occur in cases of atrophic gastritis without pernicious anemia after liver therapy. It has been suggested that in some cases atrophic gastritis may be the result of a lack of the antianemia factor without associated changes in the blood and also that a parallelism between atrophy of the tongue, of the pharynx and of the stomach and changes in the cord should be assumed. Furthermore, it has been found that in some cases of hypochromic anemia the atrophy of the mucosa has disappeared after iron therapy. According to Schindler, Kirsner and Palmer, the evidence seems to indicate that in some cases, at least, atrophic gastritis is related to a deficiency state. There is no available information to indicate that

9. Jones, C. M.: Problem of Gastrectomy and the Anemias, Am. J. Digest. Dis. **7**:502, 1940.

10. Schindler, R.; Kirsner, J. B., and Palmer, W. L.: Atrophic Gastritis: Gastroscopic Studies on the Effects of Liver and Iron Therapy, Arch. Int. Med. **65**:78 (Jan.) 1940. Schindler, R.; Nutter, P. B.; Groom, H. E., and Palmer, W. L.: Anatomic Foundation of Anacidity: Gastroscopic Study, ibid. **66**:1060 (Nov.) 1940.

the improvement in the gastric mucosa is a true histologic regeneration, for microscopic studies are not available. The fact remains, however, that the living mucosa, in cases in which there has been a response to treatment, cannot be distinguished from a normal mucosa. This observation led Schindler and his associates to employ systematic substitution therapy in 8 cases of atrophic gastritis not associated with pernicious anemia, sprue, combined degeneration of the cord or pellagra. They found that in some, but not all, of the cases liver therapy or liver and iron therapy caused the mucosa to appear normal again. It is impossible, in their opinion, to state whether the regeneration is genuine, that is, whether it is due to the formation of new glands, as microscopic examinations are necessary to settle this question. The use of liver, iron or vitamins is justified in the treatment of atrophic gastritis, according to them, but it is emphasized that additional careful studies are necessary in order to evaluate such therapy.

According to Miller,[11] the modern view concerning gastritis is that "the clinical diagnosis is justified only as a result of gastroscopic observation, though such a study at best gives one only a visual picture of the gastric mucosa." Attempts at more exact studies may be misleading, as specimens of the stomach made available by operation or necropsy are so altered that they may give erroneous information. Miller does not believe that the type of gastritis can be classified. He prefers merely to describe his observations. A brief résumé of the literature bearing on the relation between changes in the stomach and pernicious anemia is given. After reference to the older literature, he considers the work of Faber and of Hurst, who both claimed that the achlorhydria of pernicious anemia is to be explained on the basis of a gastritis. Faber expressed the belief that the gastritis produces changes in the pyloric region which bring about a suppression of the intrinsic factor and therefore is the cause of pernicious anemia. On the other hand, Meulengracht found in 8 cases of pernicious anemia that the maximal gastric alterations occurred in the fundus. They were of an atrophic nature, with disappearance of both the chief and the parietal cells. This would explain the achylia gastrica but would not account for the absence of the intrinsic factor, which is secreted mainly in the pyloric region. These observations were substantiated by those of Magnus and Ungley. The latter expressed the opinion that the fundal atrophy results perhaps from some endocrine, nutritional or congenital factor, rather than from an inflammatory change. The observations of gastroscopists indicate that the gastritis in most cases of pernicious anemia is of the atrophic type, but sometimes it is said to be hypertrophic. Both degenerative and

11. Miller, T. G.: The Relation of Gastritis to Anemias, Internat. Clin. **1**:173, 1940.

inflammatory lesions have been noted, involving on some occasions the entire mucosa and at other times only that of the fundus or the antrum. The additional evidence of the freedom of the antrum from involvement in some cases suggests that antral gastritis is not, as Faber suggested, the explanation for lack of the intrinsic factor. Furthermore, some observers have reported regeneration of the mucosa after treatment with liver. This statement has been questioned. Recent investigations have suggested that the gastric secretion in patients with pernicious anemia contains a substance, not present in normal persons or in those with cancer of the stomach, which causes suppression of the secretion of hydrochloric acid. If this is true, then the gastritis, even though it is present, may not be the cause of the achlorhydria. According to Schindler's theory of the relation of the stomach to pernicious anema, absence of an antianemia substance may produce atrophic gastritis before it causes the anemia. He stated the opinion that in pernicious anemia some factor is lacking and that this lack is responsible for the syndrome, including the inflammation and atrophy of the tongue, the pharynx, the stomach and the intestine as well as the anemia and the neural manifestations. Schindler expressed the belief also, according to Miller, that in pernicious anemia two separate conditions are present in the stomach, primarily, a dysfunction of the cells that produce the intrinsic factor and, secondarily, degeneration or atrophy of the surface epithelium. With the atrophy, he suggested that there may be superimposed inflammatory changes. In conclusion, Miller states that a review of the literature suggests that chronic gastritis, usually of the atrophic type, is commonly associated with pernicious anemia and sometimes with other forms of anemia and that it frequently precedes the alterations in the blood in addisonian anemia, but that at the same time certain recent data and opinions lead one to doubt that gastritis is the cause of pernicious anemia. He considers that there is no definitely established etiologic relationship between the two diseases

Carey [12] states that gastroscopic examination of the stomach in patients with pernicious anemia has demonstrated the presence of atrophy of a greater or less degree. Whether or not the gastric mucosa returns to normal in patients who have been treated with liver is a matter about which all observers are not in accord. The author has never seen a patient with pernicious anemia who had a normal gastric mucosa, and, moreover, he has not observed restoration of gastric mucosa to normal in any patient examined after treatment. In some there has been evidence of regeneration. After a study of 15 cases of pernicious anemia by means of the gastroscope, he concluded that this regeneration is not

12. Carey, J. B.: Gastroscopic Observations in Pernicious Anemia, Minnesota Med. **23**:311, 1940.

evidence of a return to complete normality, which would imply that the glands could again secrete hydrochloric acid and the intrinsic factor would return, neither of which processes recurs. He believes that the gastric mucosa might show gross evidence of improvement in color and even in the direction of recession of the atrophic characteristics. This is probably due to improvement in the general condition and in the blood brought about by the anti-pernicious-anemia therapy.

Relation of the Gastric Secretions to Pernicious Anemia: It has been previously shown by Taylor and his co-workers that normal gastric juice contains a proteolytic enzyme capable of hydrolyzing casein to the proteose stage in an alkaline medium, but not at hydrogen ion concentrations below 4.0. This would appear to distinguish the enzyme from pepsin, while the failure of the enzyme to produce large amounts of amino nitrogen within twenty-four hours also eliminates trypsin and erepsin. Although it cannot be proved that the proteolytic activity is identical with that of the intrinsic factor, it is of interest to note that such activity is retained or destroyed under certain circumstances which affect the clinical potency of the intrinsic factor in a similar fashion. The present publication of Gessler, Dexter, Adams and Taylor [13] is an attempt to demonstrate further resemblances of this nature. They show that the agent which is responsible for the proteolytic activity in vitro of normal human gastric juice at a p_H of 7.4 may be completely removed by adsorption with Lloyd's reagent. In this respect it resembles the so-called intrinsic factor. It has also been demonstrated that this enzyme is unable to penetrate a semipermeable membrane. Furthermore, it was found in this study that because of the usual presence of interfering enzymes from the intestine, the in vitro method was unsatisfactory for determining in cases of pernicious anemia the amount of proteolysis which could be ascribed to the proteolytic agent in normal human gastric juice.

Schenken, Stasney and Hall [14] agree with the generally accepted theory that the active anti-pernicious-anemia principle is formed by an interaction of a substance secreted by the stomach with some material in the food and that the active principle thus formed is stored in the liver. Considerable controversy has arisen, however, concerning the production and nature of this substance. It was thought that information which would have a bearing on these questions might be gained

13. Gessler, C. J.; Dexter, S. O.; Adams, M. A., and Taylor, F. H. L.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: VIII. Further Studies of the Proteolytic Activity of Normal Human Gastric Juice in Vitro; and the Limitations of the Method in Pernicious Anemia, J. Clin. Investigation **19**:225, 1940.

14. Schenken, J. R.; Stasney, J., and Hall, W. K.: Antianemic Principle in Human Liver in Carcinomas of Stomach and Cecum, Am. J. M. Sc. **200**:11, 1940.

if tests were made of the antianemia potency of the livers of patients with carcinomas which had destroyed various portions of the gastrointestinal tract. The results were as follows: The liver of a patient with scirrhous carcinoma of the pars pylorica did not contain the active principle, as indicated by its failure to produce the anticipated response when a liver extract prepared from it was administered to a patient with typical addisonian pernicious anemia in relapse. On the other hand, an extract prepared from the liver of a patient whose death was due to gastric carcinoma which involved the entire stomach, except a portion of the pars pylorica, did contain the active principle. The administration of extracts prepared from the livers of the 2 patients with carcinoma of the stomach to another patient with typical addisonian pernicious anemia in relapse confirmed the observations just described. The hematopoietic principle was present in an extract of the liver of a strikingly emaciated patient who died with carcinoma of the cecum. As it is considered that the most active part of the gastric mucosa in the production of the active principle is the pyloric region, it seems significant that the antianemia principle was found to be absent in the patient who had carcinoma involving the pyloric mucosa and that it was present in the liver of the patient whose entire stomach, except for the pylorus, was involved by the carcinoma.

Morrison [15] believes that the anti-pernicious-anemia potency of the stomach may be attributed to the fundus region, as well as to the other portions, and that this activity is ordinarily neutralized by the action of pepsin, a product primarily of the fundus. Greenspon, several years ago, advanced the theory that an extrinsic factor, as conceived by Castle, was necessary for the formation of an antianemia principle only as a protection from the inactivating effect of pepsin and that the intrinsic factor was the sole essential element. Greenspon's contention, if confirmed, would strongly support that of Morrison. The latter's studies have shown that the feeding of depepsinized whole stomach mucosa, with and without the addition of extrinsic factor, was not "significantly" effective in cases of pernicious anemia and that the feeding of depepsinized pyloric mucosa without the extrinsic factor was ineffective; when extrinsic factor was added to this, however, there was definite, but minimal, evidence of anti-pernicious-anemia activity. Greenspon's claim of higher activity by depepsinization has not been sustained, nor has his concept of the existence of an anti-pernicious-anemia principle, excluding the action of the extrinsic factor, been confirmed. Morrison suggested that it may not be possible to depepsinize fundus tissue completely and that this failure may account for the inactivity of fundus preparations. Morrison believes that the fundus may play a role in pernicious anemia.

15. Morrison, S.: Studies in Pernicious Anemia: Inquiry into Role of Pepsin, Ann. Int. Med. **14**:242, 1940.

This is suggested by (1) Greenspon's demonstration, unless disproved, of the antagonism of pepsin toward the anti-pernicious-anemia factor of Castle, (2) the known adsorptive capacity of protein for pepsin and (3) predominance of the peptic cells in the fundus. We do not necessarily agree with the reason which Morrison has advanced for the importance of the fundic glands in pernicious anemia, but attention is directed to the recent observation that it is atrophy of these glands, rather than of those in the pylorus, which is found in patients who succumb to pernicious anemia.

Bloomfield has previously made observations which indicate that the gastric secretion decreases with advancing years. This finding, however, was based on averages of many examinations on different persons, and no information was available as to what happens in the individual patient. In an attempt to answer this question, he previously reported the results of standard histamine tests repeated on the same persons after an interval of five years. Apparently, the five year period was too brief for conclusive results. Recently it was possible to reexamine 5 essentially normal people whose gastric secretions had been studied ten years previously. It was found [16] that after this interval some persons show little or no change, whereas in others there is a definite diminution. Three of the 5 showed practically identical secretions; 1 had a slight decline of acidity but not of volume, and in 1 there was a definite decrease of both volume and acid. According to the author, it is not known why some preserve their secretion unaltered over many years and others show a rapid decline. It had previously been demonstrated by Goldhamer [17] that pernicious anemia is associated not with an absence of the intrinsic factor but with a diminished amount, which may be proportional to the total volume of the gastric secretions. Since the volume may diminish with age in some persons, this relationship may be one of the factors which accounts for the greater incidence of pernicious anemia in older people.

In a discussion of Meulengracht's statement, in 1935, that atrophy of that part of the stomach which comprises the "pyloric-gland region" resulted in lack or diminution of the intrinsic factor, Weber referred to a case which he and Huber [18] now report complete in all details. At the time of the discussion, the case was considered to be one of pernicious anemia, possibly due to atrophy of Meulengracht's "pyloric-gland region," although the fundic glands were still able to secrete

16. Bloomfield, A. L.: The Decrease of Gastric Secretion with Advancing Years: Further Observations, J. Clin. Investigation **19**:61, 1940.

17. Goldhamer, S. M.: The Presence of the Intrinsic Factor of Castle in the Gastric Juice of Patients with Pernicious Anemia, Am. J. M. Sc. **191**:405, 1936.

18. Weber, F. P., and Huber, H.: Megalocytic Anemia in a Case of Jejunal Ulcer with Fatal Perforation, Acta med. Scandinav. **104**:543, 1940.

sufficient quantities of hydrochloric acid and of pepsin. The patient's condition had been classified as pernicious anemia without achlorhydria, but after the necropsy it was conceded that he could not be regarded as having suffered from true pernicious (addisonian) anemia in the modern sense of the term. The blood picture was typical of pernicious anemia; hydrochloric acid was present in the gastric secretions, and a response to liver therapy occurred. At necropsy a perforating jejunal ulcer was found.

Dr. Witts regards this case as one of megalocytic anemia secondary to jejunal ulceration, similar to numerous other cases of megalocytic anemia with associated intestinal stenosis. The authors quote Dr. L. J. Witts as follows:

> Before diagnosing pernicious anemia with normochlorhydria, I should demand complete exclusion of any pathological lesion in the alimentary tract, and also proof of the diagnosis by the Price-Jones curve, sternal puncture and stool analysis.

Sandorf and Davidhoff [19] propose that the terms pernicious and allied anemias be discarded and the designation gastric anemia be substituted. Furthermore, they would replace the name pernicious anemia with the term achylia gastric anemia and for hypochromic, commonly called secondary, anemia they would employ the term hypochlorhydric anemia. They maintain that this type of nomenclature places the proper emphasis on the functional derangement of the gastrointestinal tract in such anemias and therefore is more intelligible. We are in accord with their concluding statement, namely:

> The relationship between the function of the gastro-intestinal system and the state of the hematopoietic system should receive due recognition in both therapy and nomenclature.

Cause of the Changes in the Nervous System Occurring in Pernicious Anemia.—Wintrobe, Miller and Lisco [20] have continued their studies on the relation of the diet to the occurrence of ataxia and degeneration in the nervous system of pigs. Previously they had observed certain neural changes in growing pigs fed a simplified diet, deficient in vitamins. Further studies have shown that the deficient substance is not vitamin A, thiamine, riboflavin, or nicotinic acid and is probably not vitamin E. Neither inanition nor mineral deficiency appears to be concerned in the production of the lesions. Their experiments were carried out as follows: Forty-four pigs, with an average age of 3 weeks,

19. Sandorf, M., and Davidhoff, M.: Gastric Anemia Syndromes, J. Indiana M. A. **33**:523, 1940.

20. Wintrobe, M. M.; Miller, L. J., Jr., and Lisco, H.: The Relation of Diet to the Occurrence of Ataxia and Degeneration in the Nervous System of Pigs, Bull. Johns Hopkins Hosp. **67**:377, 1940.

were raised on a basal diet containing casein, sugar, lard, a mineral mixture, cod liver oil, ascorbic acid and varying amounts of yeast. When the yeast intake was eliminated or reduced to a low level, despite an adequate amount of thiamine, riboflavin or nicotinic acid in the diet, a condition developed which was characterized by ataxia and extensive lesions in the nervous system. These lesions consisted of degenerative changes in the peripheral nerves, the spinal ganglions, the posterior roots and the dorsal funiculi of the spinal cord. In extreme degrees of change there were also lesions of the anterior horn cells. When a filtrate factor obtained from yeast was added to the diet, less extensive changes occurred, but even when whole dried yeast was furnished in large amounts, only 5 of 12 pigs remained free from the lesions. In none of the pigs fed whole desiccated liver did changes referable to the nervous system develop. Wheat germ oil failed to prevent the neural lesions. These carefully controlled experiments are of interest for many reasons, but especially from the standpoint of the cause of the neurologic changes in pernicious anemia. They have demonstrated that a striking degenerative type of lesion of the nervous system can be produced in pigs by a dietary deficiency. While there is not general agreement concerning the cause of the changes in the spinal cord and the peripheral nerves occurring in pernicious anemia, the most likely possibility at present is the lack of some component in the diet or the inability to absorb or utilize it.

Field and associates [21] have made the interesting suggestion that the neural changes in pernicious anemia may be due to a thiamine deficiency. The lack occurs not necessarily because the dietary intake of this substance is low but because subjects with achlorhydria require a larger intake of the material than do those with normal gastric acidity. This increased demand is attributed to a phenomenon observed by him and his collaborators,[22] namely, that thiamine is destroyed in bile and pancreatic juice when these secretions are unmodified by the acid in the stomach.

Miscellaneous Clinical Observations in Cases of Pernicious Anemia.—Layne and Boyden [23] have conducted a series of studies dealing with the mechanism of emptying the gallbladder. In the first group of patients observed, it was noted that those with peptic ulcer displayed a significantly faster rate of emptying than did controls of a comparable age. This increased rate was attributed to a greater food stimulus, rather than

21. Field, H., Jr.; Robinson, W. D., and Melnick, D.: Vitamins in Peptic Ulcer, Ann. Int. Med. **14**:588, 1940.

22. Robinson, W. D.; Melnick, D., and Field, H., Jr.: Urinary Excretion of Thiamin in Clinical Cases and the Value of Such Analyses in the Diagnosis of Thiamin Deficiency, J. Clin. Investigation **19**:399, 1940.

23. Layne, J. A., and Boyden, E. A.: Evacuation of the Gall Bladder in Patients with Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **43**:534, 1940.

to an increased production of gastric juice. This interpretation was supported by observations on patients with carcinoma of the stomach, in whom it was found that a striking reduction of the amount of free hydrochloric acid failed to retard the emptying of the gallbladder. The present report is based on a study of 22 patients with pernicious anemia who were treated with liver extract. The hemoglobin of the blood either had reached normal levels or was responding to treatment. The histamine test disclosed complete absence of free acid in all patients and only minimal amounts of total acids. Of special interest was the fact that the gallbladder could be visualized in only 60 per cent of these patients, notwithstanding the use of the intravenous method of introducing the dye and the absence of any history of disease of the gallbladder. Visualization failed in only 9 per cent of the patients with ulcer and in 22.7 per cent of those with carcinoma. For the remaining 13 of the 22 patients in whom the gallbladder could be visualized, the mean curve of emptying of the gallbladder approximated that for the controls. Since there was complete absence of free hydrochloric acid in all 22 patients, even after stimulation with histamine, it must be concluded that free hydrochloric acid in the stomach is not essential in the evacuation of the human gallbladder.

Vannotti [24] reports 2 cases of pernicious anemia in which he considers that myxedema was a complication. This is an association which we have observed occasionally, but which we have thought, in all probability, existed on the basis of an incidental association. Vannotti, however, believes that there is an etiologic relationship between the two conditions. He speculates that as the iron content of the blood and tissues is elevated in cases of pernicious anemia, the tissue metabolism is stimulated. This metabolic increase, he assumes, acts on the cells of the thyroid gland, and their normal stimulus is put at rest. As a result, he concludes, myxedema might develop in some cases. To us, such a highly theoretic explanation of this association seems hardly necessary.

It is stated by Szekely [25] that anemia is occasionally associated with cardiovascular disturbances, especially with functional cardiac signs and symptoms and with angina pectoris, but there is still a wide diversity of opinion as to the frequency with which it occurs. A complete review is given of the literature dealing with the subject. Electrocardiographic studies were made in 76 selected cases of anemia in which clinical examination did not reveal any signs of disturbances of the cardiovascular system or any extracardiac conditions that might also produce electro-

24. Vannotti, A.: Anémie de Biermer et hypothyréose, Schweiz. med. Wchnschr. **16**:1106, 1940.

25. Szekely, P.: Electrocardiographic Findings in Anaemia, Brit. Heart J. **2**:1, 1940.

cardiographic changes. The material consisted of 32 cases of pernicious anemia and 44 cases of secondary anemia of the hypochromic type. It is emphasized that in the cases of pernicious anemia the patients were aged and slight sclerotic changes in the coronary arteries could not with certainty be excluded, in spite of normal clinical findings. Of the 76 selected cases of the two different types of anemia, electrocardiographic changes were found in 23. Most frequently flattening of the T wave occurred; less frequently depression of the S-T segment and low voltage were observed. A case of hypochromic anemia was reported in which inversion of the T wave in leads II and III occurred after a profuse hematemesis. The electrocardiographic changes entirely disappeared at an early stage, when only slight improvement of the anemia had been observed. The author concludes that there is not always a close parallelism between the cardiac changes and the degree of anemia. It appears to him that in acute and chronic anemia, angina pectoris or electrocardiographic changes are not merely due to the anemia causing anoxemia of the heart muscle, but in some cases to reflex vasomotor change as well. In chronic anemia, the primary myocardial anoxemia as the direct result of the diminution of the oxygen-carrying power of the blood may play a more decisive role. But besides this factor, toxic influences must be taken into consideration, as they may affect the myocardium directly.

Erf and Rhoads [26] recall that the absorption of sugar and fat in patients with sprue is improved after treatment with liver extract and that patients with pernicious anemia with a diminished rate of absorption of dextrose become normal after similar therapy. Basing their conclusion on these two observations, the authors state that there is a dysfunction of the intestinal tract which may be corrected by some constituent of liver extract. The malabsorption of dextrose and fat cannot be utilized as evidence that liver extract is absorbed imperfectly in the two diseases, for the active principle is probably a breakdown product of protein, most likely a peptide. For this reason the authors have studied the absorption of aminoacetic acid by patients with sprue or pernicious anemia, as well by those with other disorders. Their observations with the aminoacetic acid tolerance test on patients with sprue or pernicious anemia suggest that this substance is absorbed from the gastrointestinal tract in patients with pernicious anemia more slowly than in normal persons. Evidence of this abnormality was not found in the same patients after the administration of liver extract, nor was malabsorption found in patients with intractable diarrhea, severe refractory anemia or pernicious anemia in complete or partial remission, but it was present in 2 patients with cirrhosis of the liver. Since no patient with sprue or

26. Erf, L. A., and Rhoads, C. P.: Glycine Tolerance Test in Sprue and Pernicious Anemia, J. Clin. Investigation **19**:409, 1940.

untreated pernicious anemia presented evidence of abnormally increased deaminization and since no aminoacetic acid was lost from the bowel during the test, it is assumed that the flat curve for plasma amino nitrogen, observed in such patients, indicated that the absorption of aminoacetic acid was impaired. The authors conclude that the abnormalities in handling aminoacetic acid may be due to a lack of some constituent of liver extract which is not the anti-pernicious-anemia substance.

Goodall [27] comments that, obviously, childbirth cannot be common among patients with pernicious anemia, for the incidence of the disease is comparatively low until after the child-bearing age. He reports the case of a patient who was first seen in 1930, at which time she was 34 years of age. She then had the fully developed blood picture of pernicious anemia, with a red cell count of 1,500,000 per cubic millimeter and a hemoglobin concentration of 31 per cent. She was treated efficiently with various stomach and liver preparations. In 1938 she became pregnant and was delivered in January 1939. At the time of delivery the red blood cell count was 4,200,000 per cubic millimeter and the hemoglobin concentration 60 per cent. Because of retained placenta considerable blood must have been lost, for the patient went into shock and required blood transfusions. A day or so after delivery the red blood cell count was 1,900,000 per cubic millimeter and the hemoglobin concentration 48 per cent. Approximately nine months later the concentration of hemoglobin was 94 per cent.

Bigg [28] made a study of the size of the spleen in patients with pernicious anemia, as there seemed to be some difference of opinion regarding this question. Some authors stated that the spleen is palpable in 20 to 40 per cent of cases. Others reported that it is rarely enlarged. It was found to be palpable in only 3 per cent of the 200 consecutive patients with pernicious anemia examined at the Simpson Memorial Institute of the University of Michigan. In 18 of these patients on whom necropsies were performed the weight of the spleen varied from 95 to 640 Gm., the average being 265 Gm. In 17 of the 18, the spleen was larger than the commonly accepted normal weight of 150 Gm. A necropsy was done on only 1 of the patients with splenomegaly for whom the clinical diagnosis of pernicious anemia was made. This patient was found to have cirrhosis of the liver. Although the spleen in cases of pernicious anemia is usually observed to be enlarged at necropsy, it is rarely increased to the size which makes it palpable during life, as it may be increased 400 per cent and still not be felt on physical examination.

27. Goodall, A.: Successful Pregnancy in Old-Standing Pernicious Anaemia, Lancet **1**:30, 1940.

28. Bigg, E.: Spleen Size in Pernicious Anemia, Ann. Int. Med. **14**:277, 1940.

The Active Principle and Treatment of Pernicious Anemia.—Test for Potency: After reviewing the various laboratory tests for estimating the potency of various anti-pernicious-anemia preparations, Schlicke [29] concludes that they do not yield uniform or satisfactory results. A recent approach has been an attempt to influence the rate of maturation of the blood of the developing fetus, as the similarity has been pointed out between the changes which occur in the blood of a developing fetus and those which are present in the blood of an adequately treated patient with pernicious anemia. Schlicke states that if it could be demonstrated that fetal hemopoiesis can be accelerated by administration of antianemia preparations, a test of great practical importance might be available. Studies by this observer indicate that normal human gastric juice contains a substance which when administered orally to pregnant albino rats produces in the blood of a fetus a significant increase in the number of circulating erythrocytes and a decrease in their volume and diameter which can be detected at birth. This substance has no effect on the number of reticulocytes or nucleated red cells in the blood of the fetus. Its activity is enhanced by neutralization and destroyed by heating; it is claimed to be absent from the gastric juice of patients having pernicious anemia. Its presence is demonstrable in variable amounts in the gastric juice of patients with simple achlorhydria or with carcinoma of the stomach. This substance has not been identified as the intrinsic factor, nor has it been established that it accelerates maturation, although the author suggests that the increase in the number of red blood cells and a decrease in their volume and diameter might be explained as the result of the premature appearance of later generations of erythrocytes, presumably from the fetal bone marrow which has been subjected to stimulation. This, the author admits, is actually maturation in the broader sense.

Active Principle in Urine: As the normal human urine, according to Wakerlin,[30] contains a substance which is reticulocytogenic for the pigeon, rat and guinea pig and is said to be effective in the treatment of pernicious anemia, consideration was given to the possibility that the reticulocytogenic principle in urine and the hemopoietic principle in liver might be similar. This is also suggested by the observation that kidney is effective in the treatment of pernicious anemia. For this reason, the reticulocytogenic substance from normal human urine was administered orally and intramuscularly to patients with pernicious anemia. The results demonstrated conclusively that the anti-pernicious-anemia principle in liver is not excreted in significant quantities, if at all, in normal

29. Schlicke, C. P.: Blood of Newborn Rats After Oral Administration to Mother of Normal and Abnormal Gastric Juice, Am. J. M. Sc. **200**:155, 1940.

30. Wakerlin, G. E.: Effect of Reticulocytogenic Principle in Urine in Treatment of Pernicious Anemia, Arch. Int. Med. **65**:21 (Jan.) 1940.

human urine. It is also concluded that the principle in kidney which is effective when given by mouth to patients with pernicious anemia is reticulocytogenic for the pigeon but is ineffective when administered intramuscularly to patients with pernicious anemia.

Method of Assay by Increase in Red Blood Cells: The standard reticulocyte equations have been of value in estimating the clinical effectiveness of various agents in treatment of pernicious anemia, but their accuracy has been questioned by some observers. It is held by some that the increased number of reticulocytes present after treatment serves qualitatively to indicate the presence of active material in the substance used for treatment, but such an increase cannot be employed as a quantitative measure of the amount of effective material administered. This opinion is based on the apparent lack of correlation between the amount of active liver principle given and the magnitude of the reticulocyte response, on the one hand, and the extent of the erythrocyte increase, on the other. It is stated by Riddle [31] that the rise in the erythrocyte count in response to therapy would be a far simpler criterion for evaluating the effect of treatment than the reticulocyte response if the expected erythrocyte increase were expressed in as simple and as accurate a form as the standard reticulocyte equations. The study by Riddle is an analysis of the quantitative relationships existing in 600 patients with pernicious anemia between the erythrocyte counts before treatment and the increase in the erythrocytes after treatment. He concludes that the average weekly increase in the erythrocyte count at the end of two weeks of treatment had an inverse relationship to the erythrocyte level before treatment. This may be expressed in the form of an equation, which he suggests be used as a standard for the effectiveness of treatment as follows: . . . $I = 0.78 - 0.174Eo$, in which I is the average weekly increase in the erythrocyte count after two weeks of treatment and Eo the erythrocyte count before treatment, expressed as millions of erythrocytes per cubic millimeter of blood.

Adequate therapy is indicated by observed values which are equal to, or greater than, those obtained from this equation; observed values which are less than those calculated from this equation indicate inadequate treatment. The occurrence of various complicating factors, such as concurrent disease, transfusion and hemorrhage, in association with pernicious anemia invalidates the use of this standard.

In previous communications Schiødt [32] has analyzed the regeneration of red blood cells in patients with hematemesis or melena from peptic

31. Riddle, M. C.: Pernicious Anemia: Erythrocyte Response to Treatment, Am. J. M. Sc. **200**:145, 1940.

32. Schiødt, E.: Observations on Blood Regeneration in Man: V. The Rise in Hemoglobin Compared with the Rise in Erythrocytes in Patients with Hematemesis or Melena from Peptic Ulcer, and in Patients with Pernicious and Hypochromic Anemia, Acta med. Scandinav. **104**:261, 1940.

ulcer or with pernicious anemia. In patients with pernicious anemia the starting point of measurement has been the day that treatment began. In both forms of anemia, with uniform and adequate treatment, the daily rise is dependent on the lowest erythrocyte value in such a way that their relation may be expressed by the simple equation, "daily rise $\times$ K = end value of regeneration — lowest value." The regeneration rate of hemoglobin may be expressed by a similar equation, and the regeneration of erythrocytes and of hemoglobin may thus be compared. On the basis of this formula, curves showing regeneration of erythrocytes and hemoglobin in patients with hypochromic anemia, in those with hematemesis or melena from peptic ulcer and in those with pernicious anemia were constructed and compared. The author concludes that when the initial level is taken into account, the increases in the red cell count and the hemoglobin percentage correspond fairly closely in cases of hemorrhagic and in cases of pernicious anemia. In hypochromic anemia, which is secondary to chronic hemorrhage and to simple achylic anemia, however, regeneration of red cells follows the same lines as in other forms of anemia, but regeneration of hemoglobin lags far behind. It was observed that in some cases of pernicious anemia the color index falls as the blood regenerates. It is thought advisable to give iron in such cases.

Alt and Young [33] are in agreement with the generally expressed belief that parenteral liver therapy is the treatment of choice for pernicious anemia, especially when degenerative changes in the spinal cord are present. With adequate therapy, neural lesions are completely arrested and, in some cases, improvement in neurologic signs occurs. Their own studies were concerned with observations on a group of 35 patients with pernicious anemia who had received parenteral liver extract therapy exclusively for a period varying from six months to eight years, the average duration being thirty-five months. The following preparations were used: 3 cc. concentrated solution liver extract parenteral (Lederle), containing 10 U. S. P. units; 1 cc. concentrated solution liver extract parenteral (Lederle), containing 15 U. S. P. units; solution liver extract, concentrated (Lilly), 3 cc. containing 6 U. S. P. units, and parenteral liver extract, 1 cc., with no U. S. P. rating. The authors conclude that pernicious anemia can be maintained in complete remission by injections of liver extract at intervals of two to three weeks. Highly concentrated preparations are as effective as cruder ones in maintaining complete hematologic and neurologic remissions. With adequate therapy neural lesions were arrested, and frequently improvement occurred. For maintenance of the patient with pernicious anemia, a highly potent preparation should be used and the response of each person should

33. Alt, H. L., and Young, R. H.: Maintenance Treatment of Pernicious Anemia with Parenteral Liver Extract, Illinois M. J. **78**:444, 1940.

be studied. As a general rule it is advisable to give an excess of liver over the minimal requirement in order to provide a margin of safety against relapse.

Since liver therapy has been employed, it has been known that eosinophilia develops after the administration of raw liver but not after use of cooked liver. The increase in eosinophils usually varies between 20 and 40 per cent but has been known to reach as high as 74 per cent. When liver was given to patients who did not have pernicious anemia, similar eosinophilia occurred. That such a change may follow the oral use of liver extract is a controversial issue. There is no reference in the literature to its development following the parenteral use of liver extract. Allin and Meyer [34] found that of 279 patients with pernicious anemia treated at the State of Wisconsin General Hospital from 1925 to 1938, 224 received one or more forms of liver therapeutically. Patients with allergic states and parasitic infection had been excluded in each instance. Of this group of 224 patients, eosinophilia developed in 87 at some time or other. It is important to note, however, that eosinophilia of a lesser degree occurred in 24 of 45 patients in whom no allergy could be found and who had received no form of liver up to the time of discovery of the eosinophilia. Four control patients without systemic disease received a combination of liver extract and cooked liver. In only 1 did eosinophilia develop; this patient was given intramuscular injections of liver extract followed, after about seven weeks, by administration of cooked liver. Twenty-one days after intramuscular administration of liver extract had begun, the percentage of eosinophils was 7.75 per cent. Of the 5 previously untreated patients with pernicious anemia who received liver extract intramuscularly, eosinophilia developed in 1. Attempts to correlate a local dermal reaction with liver extract and the development of eosinophilia were unsuccessful. It was concluded that the allergic nature of the eosinophilia had not been demonstrated and that neither had this been excluded as a possibility. Further investigations are necessary to settle this question.

Strauss and Pohle [35] discontinued all antipernicious anemia therapy in a group of 15 patients with pernicious anemia who had been treated for about three years and whose red blood cell counts during this interval had remained continuously at 4,500,000 per cubic millimeter or higher. Previously, the patients had received 10 cc. of liver extract intramuscularly every four weeks, prepared according to the method of Strauss, Taylor and Castle. Three of the patients showed no signs

34. Allin, R. N., and Meyer, O. O.: Development of Eosinophilia Following Liver Therapy, J. Lab. & Clin. Med. **26**:457, 1940.

35. Strauss, M. B., and Pohle, F. J.: Duration of Remission in Pernicious Anemia with Liver Therapy: Efficacy of Massive Doses Administered at One Time, J. A. M. A. **114**:1318 (April 6) 1940.

of anemia until nineteen, twenty-six and twenty-seven months, respectively, after liver therapy was stopped. In the remaining 12 patients anemia developed, with a red blood cell count of 4,000,000 or less per cubic millimeter, within a period of ten months. Three of these had a relapse in two months after liver therapy was omitted. At the time of the relapse each of the 12 patients received 160 cc. of the same liver extract intramuscularly over a period of one week. This dose was 30 cc. more than the amount which had been given in divided doses over the previous period of a year, during which time the red blood cell count had remained within normal limits. After this massive dose, each patient was seen at intervals of one month. Relapse occurred again in each patient in a period varying from two to twelve months. In general, the length of the remission appeared to be a function of the individual patient rather than of the treatment. The authors conclude that the majority of patients with pernicious anemia cannot be treated safely by injections of liver extract if the period between the treatments is too long, even if massive amounts are given. Treatments should be given at one to four week intervals, depending on the individual case. The authors emphasize the obvious difficulties involved in determining the potency of liver extracts by their maintenance effects.

Strauss, Solomon and Fox [36] studied the effect of intramuscular injections of liver extract on the neural manifestations of pernicious anemia. Their report is based on a study of 85 patients, observed for an average period of seven years. The patients received intramuscularly solution liver extract (Lilly) N. N. R. prepared according to the method of Strauss, Taylor and Castle. It is estimated that this material contains about 1 injectable U. S. P. unit per cubic centimeter. It is an aqueous solution of fraction G of Cohn and contains many substances present in liver other than the anti-pernicious-anemia principle. Most of the patients received 10 cc. of this extract at weekly intervals, but others received as much as 10 cc. three times weekly and some as little as 10 cc. every three weeks. Twenty-one of the patients had severe involvement of the cord, as evidenced by spasticity or ataxia or both, resulting in definite disturbances of locomotion. Also, they had paresthesia of the hands and feet, diminution or absence of vibratory sensation in the legs and moderate to advanced muscular weakness. Impotence, which was thought to be attributable to pernicious anemia, was present in 5 patients. Girdle sensations were common. The treatment administered in this group of 21 patients with advanced changes in the cord was sufficient to prevent any objective neurologic signs from becoming more pronounced, nor did abnormal signs not previously

36. Strauss, M. B.; Solomon, P., and Fox, H. J.: Combined Degeneration of Spinal Cord in Pernicious Anemia: Results of Seven Years' Experience with Parenteral Liver Therapy, New England J. Med. **222**:373, 1940.

present appear in any of the patients with advanced involvement of the spinal cord. In other words, Strauss and his associates have demonstrated that adequate anti-pernicious-anemia therapy can completely arrest the neural manifestations of pernicious anemia. A second group who received this treatment consisted of 64 patients who did not have significant signs or symptoms of involvement of the nervous system. Over a period of seven years there was no evidence that further neural damage was done. These authors stress the fact that previous observers who stated that the neural involvement progressed despite adequate therapy did not use the proper criteria for adequate therapy. According to Strauss and his associates, treatment should be given so that the red blood cell count is maintained at a level of 4,500,000 per cubic millimeter, the mean corpuscular volume below 100 cubic microns and the color index at 1.0 or less. Furthermore, there should be no symptoms, such as glossitis or indigestion, attributable to pernicious anemia. If there should be a recurrence of the paresthesia of the extremities, the dose of the liver extract should be increased, usually doubled. If the patient presents any other symptoms which might possibly be due to changes in the spinal cord, the dose should be doubled. We are in complete accord with the concluding statement of the article:

> By means of appropriate parenteral liver extract therapy for each case, the spinal-cord lesions of pernicious anemia may be prevented from developing, or, having appeared, may be completely arrested.

Pernokis [37] gives a routine description of the symptoms and signs of the disease and the usual laboratory findings. There are some statements with which we are not in accord, of which the one indicating that the spleen is palpable in 40 per cent of cases is an example. Data concerning this organ are presented in an article by Bigg, which is cited in this review. Furthermore, the treatment suggested is inadequate as the doses are too small, and we do not consider it necessary to give hydrochloric acid or iron medication to the average patient with the disease.

Evans [38] presents an excellent review of the clinical aspects of pernicious anemia and a résumé of the development of knowledge of the disease up to the introduction of the liver treatment by Minot and Murphy, in 1926.

MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA AND THE OCCURRENCE OF THE LATTER IN THE TROPICS

Since 1932 a study of the tropical anemias as they occur in Puerto Rico has been in progress. Cases of macrocytic anemia have been

37. Pernokis, E. W.: Pernicious Anemia, Internat. Clin. **2**:216, 1940.

38. Evans, F. A.: Clinical Aspects and Treatment of Pernicious Anemia, Pennsylvania M. J. **43**:946, 1940.

observed which did not fit into the syndrome of sprue as it is most frequently seen in that region or into that of clinical pernicious, or addisonian, anemia of the temperate zones. The work of Wills on tropical anemia in India and that of Fairley and his co-workers on nutritional anemia in Macedonia suggested to Rodríguez-Molina [39] that these conditions probably fell into the category of disturbances which he designated as nutritional macrocytic anemia. He cites the unpublished observations of Hernandez Morales, in Puerto Rico, which show that in a study of the blood of 104 girls, 27 per cent were found to have macrocytic hyperchromic anemia and 28 per cent macrocytic hypochromic anemia. The anemia was mild and appeared to be correlated with a deficient diet. The case records of 2 colored women aged 60 and 48, respectively, suffering from tropical macrocytic anemia are reported. In both the anemia was severe; in 1 it was of the macrocytic hyperchromic type, whereas in the other it was of the macrocytic hypochromic variety. Although the blood pictures bore a close resemblance to those characteristic of sprue and pernicious anemia, it is thought by the author that this anemia could be distinguished from the latter two diseases. The condition is thought to be due to some deficiency of the diet, other than Castle's extrinsic factor. The parenteral use of crude liver extracts, which is effective in treatment of tropical anemia in India, is also efficacious for this type of anemia, as is autolyzed yeast extract given orally. When iron deficiency is present, iron sulfate is also recommended.

Azmy Pasha and Zanaty [40] are in agreement with the statement that pernicious anemia has a racial incidence, for it is generally regarded as a disease of the Nordic races and is less common among the southern races. According to them, it is rarely met with in Asiatics and is unknown in the tropics; its extreme rarity in Egypt has recently been emphasized. In the course of investigating many cases of anemia in Egypt, the authors encountered 1 which was thought to be an instance of true addisonian pernicious anemia. The patient was a man aged 34 who one year previously had suffered from a severe attack of diarrhea, with as many as twenty liquid stools daily. He recovered from this spontaneously and remained well for five months; then the onset of symptoms of severe anemia was followed by a recurrence of the diarrhea. The patient had a smooth, atrophic tongue and gave a history of recurrent glossitis. The spleen could be felt 1 fingerbreadth below the costal margin. Paresthesia of the limbs was the only neurologic manifestation. The red blood cell count was 1,000,000 per cubic millimeter, the hemoglobin concentration 32 per cent and the white blood cell count

39. Rodríguez-Molina, R.: Tropical Macrocytic Anemia in Puerto Rico: Report of Two Cases, Puerto Rico J. Pub. Health & Trop. Med. **15**:177, 1939.

40. Azmy Pasha, S., and Zanaty, A. F.: Pernicious Anaemia in Egypt, Lancet **2**:1359, 1939.

4,000 per cubic millimeter. After an unsuccessful trial of iron therapy and the use of a liver preparation which contained autolyzed yeast extract (marmite) and iron, the patient was given 1 pound (453 Gm.) of raw liver daily. This medication caused a prompt reticulocyte response and an increase in the erythrocyte count and the hemoglobin percentage to normal. A fractional test meal following the injection of histamine showed achlorhydria. A bone marrow puncture, which gave the first clue to the diagnosis, showed megaloblastic hyperplasia, which changed to a normocytic picture with administration of liver extract. The authors maintain that the patient did not have nutritional macrocytic anemia, as his diet was adequate and this syndrome has not been encountered in their experience in Egypt, even among the poorer classes.

Manson-Bahr [41] gives a complete review of the possible interrelationships of the clinical syndromes of pellagra, pernicious anemia, sprue, idiopathic steatorrhea and nutritional megalocytic anemia. The reader is referred to his original papers for the interesting details presented. According to the author, it has been shown that glossitis, probably of a similar nature and nonspecific to the disease, is found in each of the several diseases mentioned. This pathologic change and additional clinical features which the diseases have in common, such as alterations in the nervous system, suggest that the syndromes are closely related. On analogic and therapeutic grounds the author is inclined to regard the cause of the phenomena which are common to all as a deficiency of the vitamin G (B_2) complex. He also suggests that nicotinic acid and riboflavin may play an important part in the treatment of this group of diseases. He concludes that borderline conditions are often encountered which may embody the salient features of two or more of the group.

MICROCYTIC ANEMIAS

Hypochromic Anemia and Iron Requirements.—Experimental Studies: A comprehensive review, chiefly of contributions to the literature during the past decade, dealing with metallic elements and their relation to blood formation has been published by Schultze.[42]

Austoni, Rabinovitch and Greenberg [43] describe a technic for viviperfusion of rats and give values for the iron content of various tissues. Healthy and anemic rats receiving a standard diet under normal

41. Manson-Bahr, P. H.: Glossitis and Vitamin B_2 Complex in Pellagra, Sprue and Allied States, Lancet **2**:317 and 356, 1940.

42. Schultze, M. O.: Metallic Elements and Blood Formation, Physiol. Rev. **20**:37, 1940.

43. Austoni, M. E.; Rabinovitch, A., and Greenberg, D. M.: The Iron Content of the Tissues of Normal, Anemic, and Iron-Enriched Rats Freed from Blood by Viviperfusion, J. Biol. Chem. **134**:17, 1940.

conditions, as well as animals fed iron supplements and maintained under reduced oxygen tension, were utilized. The liver and the spleen exhibited the greatest depletion of the metal in anemic rats. The largest increase of iron occurred in the bone marrow of iron-enriched animals. Austoni and Greenberg [44] continued their studies with the aid of radioactive iron. Accumulation of the metal was demonstrated in the muscles of iron-fed anemic rats, and greater absorption of labeled iron was observed to occur in anemic than in normal animals. Twelve hours was required for the passage of a single dose of radioactive iron from the stomach through the small intestine. Passage through the alimentary tract was significantly slower in anemic rats, and the authors suggest that delayed passage may be a factor in the greater absorption by such animals. Less iron was excreted by anemic rats in both urine and feces. During a ten day period of observation normal animals retained about 30 per cent and anemic rats approximately 50 per cent of the radioactive iron administered. The greater part of the elimination occurred within forty-eight hours of administration. The specific accumulation per gram of tissue weight was greatest in the bone marrow, blood, spleen, liver and heart, whereas the largest total accumulation took place in the blood and muscle, particularly in the anemic animals. After ten days it was noted that radioactive iron was practically gone from the muscle and blood of normal rats, but 25 per cent of the administered dose remained in the muscle and 14 per cent in the blood of anemic animals.

Hahn and his associates [45] report confirmation of their previous observation that radioactive iron is detectable in circulating red blood cells of anemic dogs within four hours of its administration. They found that absorbed labeled iron was entirely converted into hemoglobin within four to seven days under standard anemic conditions. As the iron intake is increased the percentage of its absorption rapidly falls.

Interrelationships of iron, calcium and phosphorus metabolism have received consideration. Anderson, McDonough and Elvehjem [46] induced anemia in rats according to their usual procedure and placed the animals on basal diets with variable quantities of calcium, phosphorus, iron and copper. The results indicated that a low calcium-phosphorus ratio was favorable to utilization of iron. Maximum utilization occurred at a

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44. Austoni, M. E., and Greenberg, D. M.: Studies in Iron Metabolism with the Aid of Its Artificial Radioactive Isotope: The Absorption, Excretion and Distribution of Iron in the Rat on Normal and Iron-Deficient Diets, J. Biol. Chem. **134**:27, 1940.

45. Hahn, P. F.; Ross, J. F.; Bale, W. F., and Whipple, G. H.: The Utilization of Iron and the Rapidity of Hemoglobin Formation in Anemia Due to Blood Loss, J. Exper. Med. **71**:731, 1940.

46. Anderson, H. D.; McDonough, K. B., and Elvehjem, C. A.: Relation of the Dietary Calcium-Phosphorus Ratio to Iron Assimilation, J. Lab. & Clin. Med. **25**:464, 1940.

ratio of 0.45, with continued decrease as a ratio of 7.65 was approached. Within ordinary limits of ingestion, and with most types of diet, calcium appears to impede the absorption of iron, whereas phosphorus exerts a favorable effect on its absorption. Barer and Fowler [47] observed no changes in the calcium, phosphorus and nitrogen balances of 16 patients with hypochromic anemia and 3 healthy persons during the administration of medicinal iron, either by mouth or by intramuscular injection.

Limited observations on mature dogs maintained on exclusive milk diets after induction of anemia by withdrawal of blood and on the iron requirements for hemoglobin formation of growing dogs led Frost and his collaborators [48] to the conclusion that copper supplements aid in the utilization of iron. Cobalt was found to exert a stimulative effect on hematopoiesis. From a study of the total iron content of rats Otis and Smith [49] concluded that a true sex difference existed in the utilization of iron. The variation cannot be explained on the basis of differences in the weights of the two sexes. During the curative period after induction of anemia by means of a milk diet more iron was stored by female than by male rats.

Lederer [50] found that the action of hydrochloric acid and a ferment was necessary for the release of the iron contained in egg yolk. In the gastric contents of patients with hypochromic anemia associated with achlorhydria the necessary ferment was lacking. Persons with pernicious anemia appeared to possess the ferment, but the iron of egg yolk was not released by the gastric secretion because of absence of hydrochloric acid.

The ability of dogs to produce new hemoglobin and plasma proteins was measured simultaneously by Robscheit-Robbins and her associates.[51] The dogs were fed an excess of iron, and anemia was maintained by frequent bleeding. The protein content of the diet was low. It was found that when strong stimuli for the production of both new hemo-

47. Barer, A. P., and Fowler, W. M.: The Effect of Iron on Phosphorus, Calcium, and Nitrogen Metabolism, J. Lab. & Clin. Med. **26**:351, 1940.

48. Frost, D. V.; Potter, V. R.; Elvehjem, C. A., and Hart, E. B.: Iron and Copper Versus Liver in Treatment of Hemorrhagic Anemia in Dogs on Milk Diets, J. Nutrition **19**:207, 1940. Frost, D. V.; Elvehjem, C. A., and Hart, E. B.: Iron Utilization in Dogs on Milk Diets, ibid. **19**:311, 1940.

49. Otis, L., and Smith, M. C.: Further Evidence of Sex Variation in the Utilization of Iron by Anemic Rats, Science **91**:146, 1940.

50. Lederer, J.: Etude comparée de la libération du fer du jaune d'œuf par le suc gastrique de sujets normaux, de sujets atteints d'anémie hypochrome avec achylie et de sujets atteints d'anémie pernicieuse, Compt. rend. Soc. de biol. **132**: 491, 1939.

51. Robscheit-Robbins, F. S.; Madden, S. C.; Rowe, A. P.; Turner, A. P., and Whipple, G. H.: Hemoglobin and Plasma Proteins: Simultaneous Production During Continued Bleeding as Influenced by Diet Protein and Other Factors, J. Exper. Med. **72**:479, 1940.

globin and new plasma protein were present preference was given to manufacture of hemoglobin, no matter which of the food proteins tested by the authors was used.

Earlier observations on hypochromic anemia induced by diets deficient in the crystalline factor I, apparently identical with the rat antidermatitis factor, vitamin B_6 (pyridoxine), have been extended by a number of workers. Fouts, Helmer and Lepkovsky,[52] who previously reported on this deficiency anemia in puppies, were able to produce the condition in adult dogs. Hypochromic anemia resulting from lack of factor I failed to respond to administration of iron and copper. Similar observations are reported by Borson and Mettier.[53] These workers placed adult dogs on deficient diets supplemented by an excess of iron. Hypochromic microcytic anemia developed and was corrected by a daily dose of 60 micrograms of vitamin B_6 (synthetic and natural) per kilogram of body weight; however, recovery was not complete when the diet was deficient in liver filtrate factors. In such cases the addition of adsorbable factors, obtained from rice bran, failed to lead to improvement. Hogan and associates,[54] on the basis of experimental observations, believe that lack of an unrecognized fraction of the vitamin B complex may be responsible for a specific anemia induced in pigeons.

Application of vitamin B_6 therapy in cases of anemia in human beings has been carried out by Vilter, Schiro and Spies.[55] The observations were limited, but the authors demonstrated that the intravenous administration of crystalline vitamin B_6 50 to 100 micrograms in physiologic solution of sodium chloride to 3 pellagrins with macrocytic anemia and to 2 patients suffering with untreated pernicious anemia was followed by some increase in the number of circulating reticulocytes.

Determinations of total iron on 2,608 samples of blood are reported by Walker and Fitz.[56] Although the authors state that "a knowledge of the blood-iron level is proving in our experience of considerable practical interest," the impression gained from a survey of their published material indicates that the procedure, as employed, offers no

52. Fouts, P. J.; Helmer, O. M., and Lepkovsky, S.: Nutritional Microcytic Hypochromic Anemia in Dogs Cured with Crystalline Factor I, Am. J. M. Sc. **199**:163 (Feb.) 1940.

53. Borson, H. J., and Mettier, S. R.: Relief of Hypochromic Anemia in Dogs with Synthetic Vitamin B_6: Influence of "Filtrate Factors," Proc. Soc. Exper. Biol. & Med. **43**:429, 1940.

54. Hogan, A. G.; Richardson, L. R.; Johnson, P. E., and Nisbet, R. N.: Pigeon Anemia as a Deficiency Disease, J. Nutrition **20**:203, 1940.

55. Vilter, R. W.; Schiro, H. S., and Spies, T. D.: Effect of Synthetic Vitamin B_6 on the Haemopoietic System of Human Beings, Nature, London **145**:388, 1940.

56. Walker, B. S., and Fitz, R.: Clinical Observations on Blood Iron, Ann Int. Med. **14**:263, 1940.

more than a rather cumbersome approach to an expression of the hemoglobin value.

Hypochromic Anemia in Adults: The relationship of iron metabolism to anemia and its therapy is discussed by Fowler and Barer.[57] They present a résumé of their previously published experimental work and conclude that the dietary iron should approximate 12 to 15 mg. per day in order to insure adequate absorption. The three primary factors which, according to the authors, determine the need for iron are its loss by hemorrhage, its loss by excretion and formation of new iron-containing tissue. They found that the larger the dose of medicinal iron administered, the smaller was the percentage of the metal absorbed, but, within limits of toleration, the greater was the total quantity retained and utilized in formation of hemoglobin.

Further observations on blood regeneration have been published by Schiødt.[32] He found that the rates of increase of erythrocytes and hemoglobin observed in cases of pernicious anemia and of acute hemorrhagic anemia were comparable. The rise in red cells in cases of chronic hemorrhagic anemia and simple achylic anemia agreed closely with that noted in cases of the aforementioned types, but the increase in hemoglobin in cases of the latter anemias lagged far behind.

A high incidence of anemia among Chinese professional blood donors is reported by Snapper and his co-workers.[58] Leukopenia, lymphocytosis and eosinophilia were frequently observed. Inadequate nutrition, in conjunction with loss of blood, was considered a factor in the causation of the anemia. Responses were obtained to iron medication.

The syndrome of dysphagia and chronic hypochromic microcytic anemia, usually associated with achlorhydria (the Plummer-Vinson syndrome), has attracted recent attention among laryngologists. Gerlings[59] describes 6 cases of this disorder, in all of which roentgenologic examinations and in 5 of which esophagoscopic studies were made. Stenosis of the esophagus, superficial ulcerations and cicatrices were observed. In some instances stagnation of secretion occurred above the entrance to the esophagus. The author points out the possibility of precancerous lesions in this condition. Cordray[60] observed hyper-

57. Fowler, W. M., and Barer, A. P.: Iron Metabolism and Its Relationship to Anemia and Therapy, Ann. Int. Med. **14**:378, 1940.

58. Snapper, I.; Lin, S. H.; Chung, H. L., and Yu, T. F.: Anemia from Blood Donation: Hematological and Clinical Study of One Hundred and One Professional Donors, Chinese M. J. **56**:403, 1939.

59. Gerlings, P. G.: Disorders of the Mouth of the Esophagus in the Syndrome of Plummer-Vinson (Dysphagia with Anaemia), J. Laryng. & Otol. **55**: 143, 1940.

60. Cordray, D. P.: The Plummer-Vinson Syndrome, Ann. Otol., Rhin. & Laryng. **49**:160, 1940.

keratinization of the epithelium of the esophagus of rats, associated with a moderate degree of anemia, after the animals had been maintained on an exclusive milk diet for five and one-half months. No web formation was found. The author suggests that in human subjects the primary lesion is an esophageal web which interferes with nutrition and thereby leads to anemia. The prolonged low blood values, he thinks, are responsible for secondary esophageal changes, which may be precancerous. Two cases are reported by Kernan [61] as instances of the Plummer-Vinson syndrome, but the data submitted fail to substantiate this diagnosis.

The association of anemia and diaphragmatic hernia of the stomach continues to excite interest because the pathogenesis of the hemoglobin deficiency, although often related to loss of blood, is not always clear. Schiro and Benjamin [62] report a case in which gastroscopic findings included decreased prominence of rugae, some of which were abnormally red. Erosions and ulcerations were not observed, and no difference was seen in the mucosa above and that below the diaphragm. Occult blood was, however, present in the feces. Two sisters of this patient also suffered with diaphragmatic hernia. Dyke and Dyas [63] report 2 cases of diaphragmatic hernia of the stomach with hypochromic anemia. The lowered blood values are attributed by the authors to changes in the gastric mucosa rather than to hemorrhage, although occult blood was found in the stools. The anemia responded to iron therapy. The case of a patient with this condition complicated by angina pectoris is described by Ernstene and McGurl.[64] With correction of the anemia by means of iron therapy the angina disappeared.

Murphy and Damarjian [65] report a case of severe hypochromic anemia in which there was clinical evidence, supported by response to specific treatment, of both iron and riboflavin deficiency.

The almost universal incidence of anemia among the coolie population of the tea estates of Assam is discussed by Hare.[66] The anemia is usually microcytic and is attributed to prolonged dietary deficiency.

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61. Kernan, J. D.: Plummer-Vinson Syndrome: Report of Two Cases, Arch. Otolaryng. **32**:662 (Oct.) 1940.

62. Schiro, H. S., and Benjamin, J. E.: Severe Anemia Associated with Diaphragmatic Hernia, Ohio State M. J. **36**:164, 1940.

63. Dyke, S. C., and Dyas, G. E.: Herniation of the Stomach with Anaemia, Lancet **1**:119, 1940.

64. Ernstene, A. C., and McGurl, F. J.: Esophageal Hiatus Hernia Associated with Hypochromic Anemia and Angina Pectoris: Report of Case, Cleveland Clin. Quart. **7**:209, 1940.

65. Murphy, R. G., and Damarjian, E.: Riboflavin Deficiency with Idiopathic Hypochromic Anemia, Rhode Island M. J. **23**:114, 1940.

66. Hare, K. P.: Clinical Investigations into Anaemia in Assam, Indian J. M. Research **27**:1041, 1940.

Hookworm infection and malaria, although prevalent, cannot be incriminated as the sole etiologic factors. In the less common macrocytic anemias, which occur most often during pregnancy, the responsible factor is thought to be a combination of nutritional inadequacy, the presence of the fetus and the effect of chronic malaria operating on an already inefficient hemopoietic system.

The subject of anemia following gastrectomy has been reviewed by Jones.[9] Other articles of a general nature dealing with the treatment of hypochromic anemia have been published by Eckman,[67] Heck,[68] Creskoff,[69] Grove,[70] Hume [71] and others.[72]

Hypochromic Anemia in Children: Observations continued over several years on the incidence, etiologic factors and treatment of anemia associated with hookworm infection in school children are reported by Payne and Payne.[73] The administration of medicinal iron, without elimination of the parasites, was followed by rapid and striking increases in the hemoglobin value. However, if the worms were not removed a definite fall in the hemoglobin level occurred within five months after the discontinuance of iron therapy. After anthelmintic treatment alone a slow rise of hemoglobin occurred and a satisfactory level was reached in one to two years. Anthelmintic treatment supplemented by iron therapy produced the best results.

A survey of the blood status of children residing in Manchester, England, is reported by Somerford.[74] She found an incidence of anemia of 58 per cent among 201 subjects ranging in age from 10 weeks to 14 years. Lowered blood values were slightly more prevalent among boys than among girls, and the anemia was usually normocytic and normochromic. The leukocyte counts of the patients were normal. Sixteen

67. Eckman, P. F.: Indications for Use of Iron in Treatment of the Anemias, Minnesota Med. **23**:712, 1940.

68. Heck, F. G.: Iron Requirements in Childhood and Adult Life, Texas State J. Med. **36**:286, 1940.

69. Creskoff, A. J.: The Treatment of Anemias Other than Addisonian Pernicious Anemia, Pennsylvania M. J. **43**:1697, 1940.

70. Grove, W. E.: Otolaryngologic Aspects of Blood Dyscrasias, Wisconsin M. J. **39**:188, 1940.

71. Hume, W. E.: The Modern Treatment of Anaemia, Practitioner **145**:373, 1940.

72. Conferences on Therapy (From Cornell University Medical College and New York Hospital): Treatment of Blood Disorders; Microcytic Anemia, J. A. M. A. **114**:2544 (June 29) 1940.

73. Payne, G. C., and Payne, F. K.: Relative Effectiveness of Iron and Anthelmintics in the Treatment of Hookworm Anemia, Am. J. Hyg. (Sect. D) **32**:125, 1940.

74. Somerford, A. E.: Nutritional Anaemia: A Further Survey of Debilitated Children in Manchester, Brit. J. Child. Dis. **37**:1, 1940.

children suffered with microcytic and hypochromic anemia. No correlation was established between hemoglobin deficiency of the children and that observed in their mothers. Economic status and size of the family bore no evident relation to the incidence of anemia. Frequently 1 child in a family was anemic, whereas others exhibited normal blood values. Nutritional deficiency and anemia were not clearly correlated.

Crowley and Taylor [75] observed in 12 children between 6 and 12½ years of age iron-resistant hypochromic or normochromic anemia associated with a low inorganic phosphorus content of the blood, without clinical evidence of rickets. Administration of vitamin D restored the blood phosphorus value to normal in one month but had no effect on the hemoglobin level. When, however, the vitamin was given in conjunction with ferrous sulfate the hemoglobin was raised from an average of 79 per cent to one of 89 per cent (Haldane) in one month.

Congenital diaphragmatic hernia is an occasional cause of severe anemia in early childhood, and unless the possibility of this condition is borne in mind the diagnosis may easily be overlooked. The subject is discussed by Ladd and Gross,[76] and interesting cases are reported by Wolff [77] and by Grenet and his associates.[78]

Over a period of ten years 6 cases of severe hypochromic anemia were observed in young girls by Alsted.[79] No evident cause for the anemia was found, and the author ascribes its development to qualitative and quantitative deficiencies of the diet. Excellent responses were obtained to large doses of iron. The clinical and hematologic features presented by these patients fit the description of chlorosis, but the author prefers the designation of essential hypochromic anemia.

Two cases of severe anemia, occurring in a brother and sister, each at the age of 8, are reported by Hjorth.[80] The findings included hyperchromic anemia, leukopenia, thrombopenia, hemorrhagic diathesis, congenital bone deformities and hypoplasia of the bone marrow, thymus and testes. Life was maintained only by frequently repeated blood transfusions. A high incidence of congenital bone deformities was discovered in the members of the mother's family. The interesting mesoblastic anomaly arachnodactyly (Marfan's syndrome), with severe anemia, was

75. Crowley, N., and Taylor, S.: Iron-Resistant Anaemia and Latent Rickets in School Children, Arch. Dis. Childhood **14**:317, 1939.

76. Ladd, W. E., and Gross, R. E.: Congenital Diaphragmatic Hernia, New England J. Med. **223**:917, 1940.

77. Wolff, S.: Diagnostic Errors, Brit. J. Child. Dis. **37**:16, 1940.

78. Grenet, H.; Isaac-Georges, P., and Combes-Hamelle: Hernie diaphragmatique droite à forme anémique, Bull. Soc. de pédiat. de Paris **37**:420, 1939.

79. Alsted, G.: Essential Juvenile Hypochromic Anemia (Chlorosis), Nord. med. (Hospitalstid.) **7**:1338, 1940.

80. Hjorth, P.: Two Cases of Constitutional Anemia in Children, Nord. med. (Hospitalstid.) **7**:1313, 1940.

observed in a 16 year old girl by Olcott.[81] At autopsy the spleen was found to be small, but the bone marrow was described as moderately hyperplastic. The mechanism responsible for the severe hypochromic and iron-resistant anemia was obscure.

The anemias of infancy and childhood are discussed by Rittershofer,[82] who states that nutritional anemia is most common between the ages of 6 months and 2½ years. The condition, he recommends, should be treated with simple iron preparations, and he finds that the supplementary use of copper is generally unnecessary. An authoritative general article on the subject, with a useful review of the recent literature, has been published by Smith.[83]

ANEMIA IN PREGNANCY

Labate[84] studied the blood values for 19 women from the thirty-eighth week of gestation to the tenth day after confinement. After delivery increases in the erythrocyte count, hemoglobin concentration, hematocrit reading and plasma protein values were observed. It was found that when the erythrocyte count and the hematocrit values were restored to normal nonpregnant limits the value for hemoglobin averaged 9 per cent less than the lower limit of normal.

A review of the present status of information regarding anemia of pregnancy in India was published by Napier.[85] The author states that the high mortality of Indian women in childbirth is due in part to anemia. It occurs with greater frequency and severity during the second half of the year and is most pronounced in the third trimester of gestation. The incidence is slightly greater in primiparas than in multiparas. Anemia is almost always associated with edema; fever occurs in one-half the women, and albuminuria is found in 25 to 50 per cent of them. There is a relatively high incidence of splenomegaly. Three common types of anemia are described: (1) microcytic hypochromic form, attributed to diet defects or loss of blood associated with hookworm infection; (2) macrocytic hyperchromic form, believed to result from the dietary lack of substances present in autolyzed yeast and crude liver extract, not associated with achlorhydria, the indirect van den Bergh

81. Olcott, C. T.: Arachnodactyly (Marfan's Syndrome) with Severe Anemia, Am. J. Dis. Child. **60**:660 (Sept.) 1940.

82. Rittershofer, C. R.: The Anemias of Infancy and Childhood, Ohio State M. J. **36**:1309, 1940.

83. Smith, C. H.: Management of the Anemias in Infancy and Childhood, Bull. New York Acad. Med. **16**:525, 1940.

84. Labate, J. S.: Blood Studies During Pregnancy and Puerperium, Am. J. Obst. & Gynec. **39**:87, 1940.

85. Napier, L. E.; Anemia in Pregnancy in India: The Present Position, Indian J. M. Research **27**:1009, 1940.

reaction or neurologic lesions and not amenable to treatment with purified liver extract, and (3) another type of macrocytic hyperchromic anemia, with evidences of hemolysis, probably associated with chronic malaria and some nutritional deficiency.

An account of anemia of pregnancy in India is also given by Chatterjee.[86] He has observed that it is most prevalent during the rainy season, in the summer. Four stages in the development of the anemia are described: (1) normocytic, the mildest manifestation observed; (2) microcytic; (3) microcytic or normocytic but hyperchromic, and (4) macrocytic and hyperchromic. This last stage the author associates with failure of the bone marrow. The administration of iron is of value in stages 1 and 2, and liver extract is efficacious in stage 3, but it has been the usual experience that blood transfusions offer the only hope of improvement to patients suffering with anemia in stage 4. The author found the serum albumin low and the globulin (euglobin fraction) high in cases of macrocytic hyperchromic anemia. Normally, during pregnancy the blood cholesterol level is elevated, but in patients with this form of anemia lowered values were obtained. The author treated 14 patients with intramuscular injections of 2 cc. of a 5 per cent solution of cholesterol in olive oil every other day. During a course of therapy lasting about two months the average erythrocyte level rose from 850,000 to 3,500,000 per cubic millimeter. Patients serving as controls received liver extract by intramuscular injection and iron preparations by mouth, without response

A review of recent contributions to the subject of anemia in pregnancy has been published by Sodeman.[87]

HEMOLYTIC ANEMIA

No etiologic classification of hemolytic anemia is wholly satisfactory, since in many cases the cause is either obvious or entirely obscure. The clinical differentiation of such anemias as congenital and acquired, with further separation into acute and chronic forms, is serviceable, although it should be borne in mind that the same provocative agent or hemolytic mechanism may underlie varied clinical manifestations. Dameshek and Schwartz[88] have reviewed the literature dealing with acute hemolytic anemia, in conjunction with a report of 4 cases which they studied extensively. They call attention to the earlier work of French investigators, particularly Chauffard, Widal and Troisier, whose studies

86. Chatterjee, H. N.: Anemia of Pregnancy in India: Its Treatment with Cholesterol, Lancet **1**:14, 1940.

87. Sodeman, W. A.: Anemia in Pregnancy, Am. J. M. Sc. **200**:117, 1940.

88. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231, 1940.

of acute acquired hemolytic states were largely ignored by subsequent authors. Dameshek and Schwartz conclude that the association of spherocytosis, increased fragility, reticulocytosis and response to splenectomy is not pathognomonic of congenital hemolytic anemia but may occur in the acquired type and may be reproduced experimentally. Spherocytosis and increased fragility they attribute to the effects on the normal, mature red blood cells of a lytic agent. In support of this view they were able to demonstrate isohemolysins in the serum in 2 of their 4 cases. Such hemolysins were effective against cells of group O and against cells of the same group in which the hemolysins occurred. They state that splenectomy is almost universally of value in the treatment of acute acquired hemolytic anemia due to the presence of hemolysins. The operation was reported as curative in 20 of 23 cases collected from the literature. Pathologic examination of the spleens in these cases revealed three types of change: (1) multiple areas of thrombosis and infarction; (2) histiocytic proliferation, often with erythrophagocytosis and giant cell formation, and (3) congestion of the pulp. Extreme normoblastic hyperplasia of the bone marrow was a general finding.

The nonspecificity of spherocytosis and decreased erythrocyte resistance to hypotonic solutions of sodium chloride in chronic hemolytic anemia of the congenital or familial type are also emphasized by Tigertt and Hill.[89] They state, furthermore, that these abnormalities are not requisite to the diagnosis of such anemia. Tigertt, Duncan and Hight [90] were able to produce microspherocytosis and increased erythrocyte fragility in dogs by the injection of specific hemolysins. Bimodal frequency distribution curves for erythrocyte diameter were obtained. Such curves are explained by the simultaneous occurrence of small spherocytes and large reticulocytes and have been observed also by Dameshek.

Whatever the role of splenectomy may be in effecting cessation of abnormal destruction of red cells, whether one of simple removal of erythroclastic cells or one of elimination of the site of hemolysin formation, evidence accumulates that the value of the operation is not limited to cases in which microspherocytosis and increased fragility are exhibited. Such a case is reported by Farrar, Burnett and Steigman.[91] In that

89. Tigertt, W. D., and Hill, J. M.: New Concepts of the Etiology of Hemolytic Anemia and Their Relation to Diagnosis, Texas State J. Med. **36**:214, 1940.

90. Tigertt, W. D.; Duncan, C. N., and Hight, A. J.: Erythrocyte Morphology in Experimental Hemolytic Anemia as Induced by Specific Hemolysin, Am. J. M. Sc. **200**:173, 1940.

91. Farrar, G. E., Jr.; Burnett, W. E., and Steigman, A. J.: Hemolysinic Anemia and Hepatic Degeneration Cured by Splenectomy, Am. J. M. Sc. **200**:164, 1940.

instance a specific hemolysin was demonstrated. Hurley and Moore[92] cured by splenectomy a 33 year old man who had suffered from intermittent jaundice and anemia all his life, although the erythrocytes were normal in shape and in their response to hypotonic solutions of sodium chloride.

The cases of a series of patients with the classic characteristics of congenital hemolytic jaundice are reported by Sharpe.[93] Of 28 patients, 11 were males and 17 females; their ages ranged from 3 to 63 years, and the onset of symptoms was usually before the age of 20. Thirteen patients underwent splenectomy, and in each case the operation was followed by recovery from anemia and jaundice. Seventeen cases of chronic hemolytic jaundice are discussed by Navarro and Cruz.[94] In two thirds of them increased erythrocyte fragility was demonstrated.

A résumé of his earlier observations and conclusions relating to hemolytic anemia is given by Haden.[95] He also describes the cases of a mother and 2 children suffering with icterus, reticulocytosis and hemoglobinemia. The red cells of these patients exhibited no spherocytosis and no decreased resistance to hypotonic solutions of sodium chloride, but they were said to hemolyze more readily than normal cells under other, unstated laboratory conditions. The mother's mother was said to have died in early life of jaundice, anemia and splenomegaly. Haden also discusses the Marchiafava-Micheli type of hemolytic anemia. This disorder and that manifested in the cases reported he ascribes to a qualitative defect, other than abnormality of shape, inherent in the erythrocyte. Haden states that hemoglobinemia and hemoglobinuria are evidence of intravascular hemolysis and that their presence contraindicates splenectomy. However, in the opinion of Dameshek and Schwartz, free hemoglobin in the plasma and urine may result from higher concentration of the same hemolysin which in other cases may give rise to urobilinuria, bilirubinemia, spherocytosis and increased fragility. Since evidence indicates that in many cases the spleen is concerned with the production of such hemolysins, intravascular hemolysis should not constitute the sole grounds for foregoing splenectomy.

The appearance of rouleaux in fresh unmodified blood may be of diagnostic aid in cases of hemolytic anemia, according to Dameshek.[96]

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92. Hurley, A. G., and Moore, W. C.: Congenital Hemolytic Jaundice: Report of a Case with Normal Fragility and Normal Reticulocyte Count, Cured by Splenectomy, Ann. Surg. **112**:392, 1940.

93. Sharpe, J. C.: Hemolytic Jaundice: A Clinical Analysis of Twenty-Eight Cases, Ann. Int. Med. **14**:953, 1940.

94. Navarro, R. J., and Cruz, J. R.: Hematologic Findings in Chronic Hemolytic Anemia (Familial Jaundice), J. Philippine M. A. **20**:566, 1940.

95. Haden, R. L.: Hemolytic Anemia, J. Lab. & Clin. Med. **26**:65, 1940.

96. Dameshek, W.: Rouleaux Formation in Fresh, Unmodified Blood as a Diagnostic Test for Hemolytic Anemia, New England J. Med. **221**:1009, 1939.

Spherocytosis is associated with short, bizarre rouleaux, and the increased thickness of some of the cells is apparent.

Increased endogenous metabolism of uric acid, a consequence of accelerated destruction of red cells, has suggested to numerous observers that the occasional association of gout and hemolytic jaundice is more than coincidental. Between 1934 and 1939, according to Deitrick,[97] there were observed in the New York Hospital 22 patients suffering from gout without jaundice and 24 patients with congenital hemolytic jaundice. Three patients suffering from both diseases were encountered. Of these 3, 2 had nephritis and died in uremia and 1 underwent splenectomy and obtained complete relief from both hemolytic anemia and gout during a subsequent seven year period of observation. Lambie [98] reports the case, with unusually complete and detailed studies, of a man of 20 who had suffered with anemia from birth and had his first attack of gout at the age of 14. The anemia was of hemolytic type, but spherocytosis and increased fragility were not found. Splenectomy was followed by remission, with subsequent exacerbation, of the anemia. The author reviews the literature, including reported instances of gout in association with other blood disorders, particularly leukemia and erythremia.

The hemolytic action of sulfanilamide and its derivatives is well recognized. Why red cell destruction occurs much more readily and proceeds to far greater lengths in some patients than in others is not understood. A Negro, observed by Spence and Roberts,[99] received 28 Gm. of sulfanilamide over a five day period in the treatment of a gonorrheal perineal abscess. The red cell count declined to 1,240,000 per cubic millimeter and the hemoglobin concentration to 21 per cent; 52 per cent of the erythrocytes were reticulated. The leukocytes numbered 140,000 per cubic millimeter, and myeloblasts and myelocytes were observed. The patient recovered. Ravid and Chesner [100] report the case of a 79 year old man, suffering from pneumonia, who was given a total of 8 Gm. of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine)

97. Deitrick, J. E.: The Association of Congenital Hemolytic Icterus and Gout, Internat. Clin. **3**:264, 1940.

98. Lambie, C. G.: A Study of Juvenile Gout in a Patient Suffering from Chronic Erythronoclastic Anemia of Obscure Origin, Together with Observations upon the Physical State of Uric Acid in the Blood and the Effects of Splenectomy, M. J. Australia **1**:535, 1940.

99. Spence, H. M., and Roberts, G. M.: Extreme Leukocytosis and Acute Hemolytic Anemia Associated with the Administration of Sulfanilamide: Report of a Case, New England J. Med. **222**:874, 1940.

100. Ravid, J. M., and Chesner, C.: A Fatal Case of Hemolytic Anemia and Nephrotic Uremia Following Sulfapyridine Administration, Am. J. M. Sc. **199**: 380, 1940.

in two days. The sequence of events which followed included jaundice, anemia, hematuria, hemoglobinuria, anuria and uremia. The patient died sixty-five hours after administration of sulfapyridine. Necropsy revealed blocking of the renal tubules with hemoglobin derivatives, a condition frequently observed after transfusions of incompatible blood. A similar fatality following the administration of 25 Gm. of sulfanilamide in the treatment of erysipelas was reported by Tragerman and Goto.[101]

Hemolytic anemia has been induced in rats by the administration of sulfanilamide, as reported by Higgins and Machella,[102] and in rabbits by ingestion of indole, as reported by Taylor.[103]

SICKLE CELL ANEMIA

Conditions affecting the sickling phenomenon in vivo and in vitro have been studied by Sherman.[104] He observed acceleration of sickling in the presence of increased leukocyte concentration, elevation of temperature and bacterial contamination, whereas the change was retarded by dilution of blood with an isotonic solution of sodium chloride and by increased oxygen tension. Sickle cells were found regularly in high percentage in the venous circulation of patients with sickle cell anemia, but not of those with the sickling trait in the absence of anemia. When anemia was present the percentage of sickle cells was always greater in the venous than in the arterial circulation. It was found that the following solutions were equally efficacious as fixatives of the sickle cell: a 10 per cent concentration of solution of formaldehyde U. S. P. in physiologic solution of sodium chloride, Zenker's stock solution, and Zenker's stock solution prepared with glacial acetic acid and with solution of formaldehyde U. S. P. Sherman describes a granular, or "holly wreath," type of cell occurring in the blood of persons with sickle cell anemia or the sickling trait. He differentiates the anemia from the trait by the following criteria: 1. The trait becomes evident only at much lower oxygen tension than does the anemia. 2. In the anemia, but not in the presence of the trait, sickle cells are found in the venous circulation and in blood placed in solution of formaldehyde U. S. P. (1:10) under oil

101. Tragerman, L. J., and Goto, J. M.: Fatal Reactions to Administration of Sulfonamide Drugs: Report of Five Cases, J. Lab. & Clin. Med. **25**:1163, 1940.

102. Higgins, G. M., and Machella, T. E.: The Bone Marrow of Rats Made Anemic by Administration of Sulfanilamide, Anat. Rec. **75**:529, 1939.

103. Taylor, W. T.: Blood Changes Produced in Rabbits by Indol, M. Ann District of Columbia **8**:362, 1939.

104. Sherman, I. J.: The Sickling Phenomenon, with Special Reference to the Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, Bull. Johns Hopkins Hosp. **67**:309, 1940.

Detection of the sickle cell trait has received the attention of Diggs and Pettit.[105] For general purposes they recommend the method of Scriver and Waugh, in which after stasis is induced in a finger a drop of blood is removed and examined in a moist sealed preparation.

The occurrence of sickle cell anemia in an Italian family of Sicilian origin is reported by Greenwald and Burrett.[106] Twenty-three members of the family were examined; of these, 5 were found whose erythrocytes underwent sickling and 2 suffered with actual anemia.

Skoog [107] reports the case of a 34 year old Negro with sickle cell anemia in whom complete hemiplegia developed, with persistent motor aphasia and palsy of several cranial nerves. The blood and spinal fluid gave negative results when tested for evidence of syphilis. The author attributes the multiple cerebral lesions to the occurrence of thromboses induced by the sickle cell abnormality. The subject of involvement of the nervous system in sickle cell anemia is reviewed by Hughes, Diggs and Gillespie.[108] They discuss in detail 25 cases previously reported in the literature and add 6 new cases, in 2 of which necropsy was done. They conclude that involvement of the central nervous system is a frequent complication of sickle cell anemia and that the prognosis is poor, although the course is unpredictable. The location of the lesions and the clinical manifestations are variable; the onset is often sudden and may be characterized by convulsions, meningeal signs, pain, aphasia, paralyses, coma and death. It is the authors' opinion that the lesions are primarily intravascular and due to thrombosis, which has followed extensions of the thrombotic process and hemorrhagic, degenerative and atrophic changes.

Cummer and LaRocco [109] point out that sickle cell anemia should be considered as a possible explanation for chronic ulcers on the legs, especially in young persons. Ulcers in patients with sicklemia, they state, are limited almost entirely to those who have actual anemia.

ERYTHROBLASTIC AND RELATED ANEMIAS

Three cases, each illustrative of a form of erythroblastic anemia, are reported by Wang and Khoo.[110] All occurred in Chinese infants and

105. Diggs, L. W., and Pettit, V. D.: A Comparison of Methods Used in the Detection of the Sickle Cell Trait, J. Lab. & Clin. Med. **25**:1106, 1940.

106. Greenwald, L., and Burrett, J. B.: Sickle-Cell Anemia in a White Family, Am. J. M. Sc. **199**:768, 1940.

107. Skoog, A. L.: Cerebral Complications in Sickle Cell Anemia, South. M. J. **33**:714, 1940.

108. Hughes, J. G.; Diggs, L. W., and Gillespie, C. E.: The Involvement of the Nervous System in Sickle Cell Anemia, J. Pediat. **17**:166, 1940.

109. Cummer, C. L., and LaRocco, C. J.: Ulcers of the Legs in Sickle Cell Anemia, Arch. Dermat. & Syph. **42**:1015 (Dec.) 1940.

110. Wang, C., and Khoo, F.: Hemolytic Anemia with Erythroblastaemia: A Report of Three Cases Seen in Chinese Infants, Chinese M. J. **58**:177, 1940.

were characterized by anemia with erythroblastemia, reticulocytosis, leukocytosis, active erythropoietic hyperplasia of the bone marrow, increased fecal urobilin, splenomegaly and hyperplastic changes in the skull. One patient suffered with nutritional deficiency and chronic infection and recovered after appropriate therapy (von Jaksch's type). The outcome in the other 2 cases was fatal, although blood transfusions were of transient benefit; in 1 of them the features of erythroblastosis foetalis were exhibited, whereas in the other the condition was suggestive rather of Cooley's anemia.

Severe anemia, reticulocytosis, bilirubinemia, urobilinemia and splenomegaly characterized the 3 cases described by Abt.[111] In 1 case the patient was 4 months old, and in the other 2 the children were each 1 year of age. Increased erythrocyte fragility and spherocytosis were not observed. The author states that the disorder may be familial but is not hereditary and that the mechanism of hemolysis is unknown. He considers transfusions of value as temporary aids and removal of the spleen as usually curative. Two of Abt's patients underwent splenectomy, with subsequent recovery.

Wayman[112] observed 2 infants, a sister and a brother, born a year apart, both suffering with icterus gravis and erythroblastemia. The first born died, whereas the second recovered after treatment with vitamin K, given because of evidence of obstructive, as well as hemolytic, jaundice and hemorrhagic manifestations.

During the past year there have appeared an unusual number of general discussions and reviews dealing in part with the erythroblastic anemias of infancy.[113] Of these the article by Smith[113h] is outstanding for its scholarly and informed treatment of a complex subject.

In 1938 Barrett[114] described an erythrocyte variant characterized by unusual thinness, increased resistance to hypotonic solutions of sodium

111. Abt, A. F.: Hemolytic Disease in Infants, Am. J. Dis. Child. **60**:812 (Oct.) 1940.

112. Wayman, E. W.: Erythroblastosis in Icterus Gravis Neonatorum Successfully Treated with Vitamin K, J. Pediat. **17**:806, 1940.

113. (*a*) Tyson, R. M.: Blood Dyscrasias of Infancy and Childhood, Mississippi Doctor **17**:589, 1940. (*b*) Atkinson, F. R. B.: Lederer's Anaemia, Brit. J. Child. Dis. **37**:35, 1940. (*c*) Dwyer, H. L., and Neff, F. C.: Anemia of the Newborn, South. M. J. **33**:246, 1940. (*d*) Ruiz, C.: Anemia idiopática del recién nacido, Arch. argent. de pediat. **11**:65, 1940. (*e*) Wellmeier, H.: Blood Dyscrasias of Infancy and Childhood, Ohio State M. J. **36**:1078, 1940. (*f*) Reading, B.: Anemias of the New Born Period, Texas State J. Med. **36**:405, 1940. (*g*) Anemias of the Newborn (Symposium), Internat. M. Digest **36**:247, 1940. (*h*) Smith, C. H.: The Anemias of Early Infancy, J. Pediat. **16**:375, 1940.

114. Barrett, A. M.: Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline, J. Path. & Bact. **46**:603, 1938.

chloride and a target-like appearance in dried blood films, due to concentric dark and light zones. The occurrence of this cell is not limited to a single clinical disorder, but it is possible that those conditions in which it is found are due to related abnormalities of erythrocyte structure. Interesting publications dealing with this subject have recently appeared. Wintrobe and his associates [115] report the observation in 14 persons, members of 3 Italian families, of a chronic disturbance of erythropoiesis characterized by microcytosis and hypochromia, bizarre red cell forms and increased resistance to hypotonic solutions of sodium chloride. In 8 subjects target cells were found. Three generations in one family and two in another were affected. The authors discuss the probable relationship of this condition to Cooley's anemia, sickle cell anemia and congenital hemolytic jaundice. As in Cooley's anemia, there appears to be an inherited defect in the production of erythrocytes whereby corpuscles are formed with an adequate or excessive membrane enclosing little substance. Other changes in the blood are attributed to attempts at compensation for the faulty red cell formation. In a footnote to their article they report observing a child with typical Cooley's anemia. Both of the child's parents were found to have target cell anemia.

Dameshek [116] reports the case of an Italian youth aged 20 who was known to have suffered with hemolytic anemia and splenomegaly since the age of 5. Generalized osteoporotic changes were found, with thickening of the skull and a bony rib tumor. Many of the red cells were of the target type, extremely thin, with a tendency to buckle and ability to withstand hemolysis at exceedingly low concentrations of sodium chloride. Nucleated erythrocytes were not seen. The author believes that target cell anemia may be a late and relatively mild form of Cooley's anemia. He considers that these conditions, together with sickle cell anemia, form a group in which target cells and increased resistance to hypotonic solution of sodium chloride are the common denominators. None of these types of hemolytic anemia is benefited by splenectomy.

A detailed case report of a patient exhibiting severe hemolytic anemia, with 47.5 per cent of the red cells of the target type, is given by Fairley.[117] The fragility of the erythrocytes was decreased. Some degree

115. Wintrobe, M. M.; Matthews, E.; Pollock, R., and Dobyns, B. M.: A Familial Hemopoietic Disorder in Italian Adolescents and Adults, Resembling Mediterranean Disease (Thalassemia), J. A. M. A. **114**:1530 (April 20) 1940.

116. Dameshek, W.: "Target Cell" Anemia: Anerythroblastic Type of Cooley's Erythroblastic Anemia, Am. J. M. Sc. **200**:445, 1940.

117. Fairley, N. H.: A Peculiar Haemolytic Hypochromic Anaemia Associated with Post-Malarial Splenomegaly of Banti's Type, Tr. Roy. Soc. Trop. Med. & Hyg. **34**:173, 1940.

of hemopoietic response was obtained after the intramuscular injection of crude liver extract supplemented by the oral administration of medicinal iron, although the use, in conjunction, of refined concentrated liver extract and iron had been of no value. Splenectomy was followed by an exacerbation of the anemia. No hemolysins were demonstrated in the blood of this patient. The author suggests that the hemolytic process was due the the "escape of an intracellular lytic enzyme into the blood stream from pathological reticulo-endothelium following prolonged chronic malarial infection."

BANTI'S SYNDROME

During 1940 there appeared several important contributions to the understanding of the pathogenesis of the disorder described by Banti as splenic anemia. Thompson [118] and Rousselot [119] report conclusions arrived at during the observation of 137 cases of this disorder encountered in ten years at the spleen clinic of the Presbyterian Hospital, New York. Only the general conclusions of these authors can be given here, and the reader is referred to the original articles for the evidence on which they are based. Thompson and Rousselot deny the validity of the classic concept of the course of Banti's disease—a primary splenic enlargement progressing through stages of anemia, leukopenia and susceptibility to hemorrhage from varices and terminating in hepatic cirrhosis. They find evidence of portal vein hypertension in all cases of this disorder, and they attribute the splenomegaly, collateral circulation and esophageal varices to a difference between the portal and the peripheral venous pressure. Portal vein hypertension, according to them, may arise from a variety of demonstrable mechanical causes, which may be intrahepatic or extrahepatic. Rousselot states that in "cases of congestive splenomegaly due to extrahepatic obstructive lesions, the prognosis and variations in clinical behavior are dependent on two factors: (1) the site of the obstructive lesion and (2) variants in the anatomy of the venous pattern."

Ravenna [120] agrees with the aforementioned authors in attributing Banti's splenomegaly to splenic congestion, but he states that the congestion is not dependent on an obstructive factor in the portal venous bed. In his opinion, it is due to primary lesions of the small splenic

118. Thompson, W. P.: The Pathogenesis of Banti's Disease, Ann. Int. Med. **14**:255, 1940.

119. Rousselot, L. M.: The Late Phase of Congestive Splenomegaly (Banti's Syndrome) with Hematemesis but Without Cirrhosis of the Liver: Further Observations on Etiology of Banti's Syndrome and Effect on Prognosis of Certain Variations in Portal Venous Pattern, Surgery **8**:34, 1940.

120. Ravenna, P.: Banti Syndrome (Fibrocongestive Splenomegaly): Definition, Classification and Pathogenesis, Arch. Int. Med. **66**:879 (Oct.) 1940.

arteries, which regulate the blood flow into the spleen. He describes the spleen as an elastic rather than a contractile organ and as an automatic controller which regulates the pressure of the splenic venous blood and the amount of blood which can be discharged through the hepatic resistance. Congestive splenic enlargement is, therefore, according to this author, a mechanism to counterbalance either an increased volume of portal blood or an increased peripheral resistance to the discharge of a normal amount of blood. Splenic changes in Banti's disease he attributes to the lesions of the splenic arterioles, the regulatory power of which becomes insufficient to control the inflow of blood. The consequent congestive splenomegaly is the cause of the circulatory disturbance in the portal bed. Secondarily, hepatic cirrhosis and venous thrombosis may aggravate the disordered state of the portal circulation.

Herliky [121] reports the case of a woman aged 30, believed to have Banti's disease, who suffered repeated hematemeses before the development of splenomegaly. Wentz and Kato [122] observed a 6 year old girl with progressive splenomegaly, anemia, leukopenia, gastric hemorrhage, terminal jaundice and ascites. Necropsy revealed primary carcinoma of the liver.

Observations on the value of splenectomy in the treatment of Banti's disease have been published by Barg and Dulin.[123] Of 43 patients seen during an eighteen year period, splenectomy was performed on 22, with an operative mortality of 27 per cent. The group of surgically treated patients is not entirely comparable to the group not given surgical treatment, and the criteria on which the decision in favor of splenectomy was based are not stated. The average age of the surgically treated patients was 35 years, and that of patients on whom no operation was performed was 43 years. The authors feel that duration of life was prolonged by splenectomy, although it is doubtful if the data presented support this conclusion.

POLYCYTHAEMIA VERA

Graham,[124] in reviewing some of Osler's early publications, commented on his fundamental understanding of the clinical aspects, as well as the pathologic physiology, of polycythaemia vera. Osler expressed the opinion that the symptoms and signs which characterize the disease

121. Herliky, J. D.: Repeated Haematemeses Associated with Banti's Disease of "Conceded" Type, M. J. Australia **2**:759, 1939.

122. Wentz, V. B., and Kato, K.: Primary Carcinoma of the Liver, with Banti's Syndrome, J. Pediat. **17**:155, 1940.

123. Barg, E. H., and Dulin, J. W.: Splenectomy in the Treatment of Banti's Syndrome, Arch. Surg. **41**:91 (July) 1940.

124. Graham, D.: Erythraemia–Polycythaemia Rubra Vera, Canad. M. A. J. **42**:281, 1940.

were due to increased viscosity of the blood and to decreased blood flow. Compensatory erythremia, which is often difficult to differentiate from true polycythemia, may, according to Hallock,[125] be distinguished on the basis of the blood volume, the red cell mass and the plasma volume. The figures for these quantities were all higher in persons with polycythaemia vera than in normal persons. In those with erythremia related to congenital heart disease, although the red cell mass and the total blood volume were increased, the plasma volume per kilogram of body weight was decreased. Hallock interpreted these results as indicating that the increased red cell volume is a compensatory mechanism to maintain blood volume and oxidation. Bassen and Abel [126] described several cases of pseudopolycythemia due to dehydration. They also emphasized the importance of determining the cell mass for diagnostic purposes. In addition, they pointed out that obesity rarely occurs in cases of polycythaemia vera.

Although polycythemia is rather uncommon, Dameshek and Henstell [127] suggested that it occurs more often than is suspected and that the apparent rarity is due in part to lack of recognition. They feel that the disease may masquerade for years and that to make the diagnosis it is necessary to take a careful history and to make a thorough physical examination and complete laboratory studies. Dameshek and Henstell describe several cases of polycythaemia vera, with many different outstanding symptoms, and classify them according to the systems involved. In analyzing their group of cases, the authors noted that symptoms due to disease of the central nervous system predominated. Other common symptoms were those due to involvement of the gastrointestinal tract and the cardiovascular system. The following signs are important: plethora of the face; purple lips; congested conjunctival blood vessels; red ears; beefy red hands and, less commonly, beefy red feet; distended retinal vessels, blue in color; purplish tongue, large and thickly coated; palpable liver and spleen, and an elevated blood pressure. The outstanding laboratory findings are increases in hemoglobin concentration, red cells, white cells (especially polymorphonuclear neutrophils), platelets and blood volume. The bone marrow shows generalized hyperplasia of all the elements (panmyelosis). In conclusion, Dameshek and Henstell suggest that the best form of treatment is phlebotomy and an iron-poor diet.

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125. Hallock, P.: Polycythemia of Morbus Caeruleus (Cyanotic Type of Congenital Heart Disease), Proc. Soc. Exper. Biol. & Med. **44**:11, 1940.

126. Bassen, F. A., and Abel, H. A.: Pseudo-Polycythemia, J. Mt. Sinai Hosp. **6**:322, 1940.

127. Dameshek, W., and Henstell, H. H.: The Diagnosis of Polycythemia, Ann. Int. Med. **13**:1360, 1940.

The peripheral vascular disturbances which occur in polycythemia are emphasized by Zeiter.[128] He noted that the symptoms may be vague for several years and are remittent in type, though progressive. The vascular complications, which he observed in 29 per cent of the cases, usually occurred in older people. The author suggested several types of treatment, including the administration of acetylphenylhydrazine, roentgen irradiation, administration of arsenic and periodic phlebotomy, in order to maintain the red cell mass slightly below normal. Fetterman and Spitler[129] pointed out that among the many factors which may cause vascular disorders of the peripheral nerves, polycythaemia vera is not unusual. The symptoms in general are dependent on the nerve involved, the extent of the pathologic changes and the general status of the patient.

The therapy of polycythaemia vera is not specific and is often unsuccessful. Pierson and Smith[130] treated 5 patients with polycythemia by the spray method of roentgen irradiation. The detailed procedure is accurately described. In 4 cases remissions were obtained which lasted twenty-three, fourteen, ten and seven months, respectively. The authors condemn the use of acetylphenylhydrazine, as well as phlebotomy, and state that the spray method of roentgen therapy is most satisfactory. As mentioned previously, both Dameshek and Henstell[127] and Zeiter[128] recommend phlebotomy as the method of choice. Stenstrom and his co-workers[131] treated 4 patients with polycythaemia vera by roentgen irradiation over the areas of the pylorus and Brunner's glands. No changes were observed in the peripheral blood, and it is the opinion of these investigators that this method has no value. In the "Conferences on Therapy" related to the treatment of the blood disorders,[132] it was the consensus that radiation, acetylphenylhydrazine and solution of potassium arsenite U. S. P. were beneficial but slow in action and should be used in conjunction with phlebotomy. Haden[133] states that the best method of treatment is phlebotomy.

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128. Zeiter, W. J.: Peripheral Vascular Disturbances in Polycythemia, M. Clin. North America **24**:485, 1940.

129. Fetterman, J. L., and Spitler, D. K.: Vascular Disorders of Peripheral Nerves, J. A. M. A. **114**:2275 (June 8) 1940.

130. Pierson, J. W., and Smith, C. D.: Treatment of Polycythemia Vera by Roentgen Irradiation of Entire Body, Am. J. Roentgenol. **43**:577, 1940.

131. Stenstrom, K. W.; Hallock, P. H., and Watson, C. J.: Negative Results of Irradiation Therapy of the Pylorus and Brunner's Gland Area in Patients with Polycythemia Vera, Am. J. M. Sc. **199**:646, 1940.

132. Conferences on Therapy: The Treatment of Blood Disorders; Polycythemia, Hodgkin's Disease and Splenic Disorders, J. A. M. A. **115**:297 (July 27) 1940.

133. Haden, R. L.: Treatment of Polycythemia Vera, Cleveland Clin. Quart. **7**:166, 1940.

Many interesting animal experiments concerned with the etiologic factors in polycythemia have been performed. Adamson and Storey [134] injected into rats (maintained on a milk diet) gastric juice obtained from patients with various blood dyscrasias. They noted an increase in reticulocytes after the injection of normal gastric juice and an added response after stimulation with histamine. Injections of gastric juice from patients with pernicious anemia induced no such response. Histamine alone produced a reticulocyte response. When gastric juice obtained from a patient with polycythemia was injected, a maximum reticulocyte response occurred, with no subsequent increase following the administration of histamine. The authors conclude from these results that patients with polycythemia may have an excess of histamine, which produces the high red cell count, or they may be sensitive to the drug.

The relationship between polycythemia and tumors in rats was investigated by Allen.[135] Polycythemia was produced and maintained by multiple transfusions. The author concludes that polycythemia per se does not inhibit tumor growth and that the changes which occurred in the tumors were due to congestion.

Brewer [136] made a statistical study of cobalt polycythemia in dogs. He noted no symptoms in his animals for at least one month with doses as high as 30 mg. per day per kilogram of body weight. If the cobalt was increased to 50 mg. daily, symptoms occurred in two weeks. The hemoglobin content was increased with daily amounts of 5 mg.; the red blood cell count increased on a daily dose of 10 mg., and the hematocrit reading was altered after somewhat larger doses.

Factors affecting the maintenance of cobalt polycythemia in rats were studied by Anderson and his colleagues.[137] They noted that daily fluctuations in counts could be eliminated if they severed the lateral vein of the tail of the rat instead of cutting off the tip when drawing samples of blood, thus eliminating the disturbing factor of hemorrhage. Employing this technic, the authors noted that when whole liver, powdered liver extract or pernicious anemia concentrate was added to the basic milk diet a higher level of red cells was produced and maintained. They further observed that casein had only a slight effect and liver residue none. If the calcium-phosphorus ratio was reduced to 0.6 by

134. Adamson, W. B., and Storey, J. E.: Observations on the Etiology of Polycythemia Vera, Texas State J. Med. **36**:26, 1940.

135. Allen, F. M.: Transfusions and Polycythemia in Normal and Tumor-Bearing Rats, J. Lab. & Clin. Med. **25**:471, 1940.

136. Brewer, G.: A Statistical Study of Cobalt Polycythemia in Dog, Am. J. Physiol. **128**:345, 1940.

137. Anderson, H. D.; Underwood, E. J., and Elvehjem, C. A.: Factors Affecting the Maintenance of Cobalt Polycythemia in Rat, Am. J. Physiol. **130**:373, 1940.

the addition of sodium biphosphate (NaH_2PO_4), the rate of development of polycythemia increased, the cobalt was more toxic and there was a depression of growth.

The mechanism of development of cobalt polycythemia in dogs was also investigated by Davis.[138] He noted that the combination of cobalt and anoxia had an added effect in producing polycythemia. The addition of ascorbic acid to the diets depressed development of the cobalt polycythemia, but not that of the anoxia type. In animals with cobalt polycythemia the ascorbic acid content of the blood was diminished. The author believes that cobalt produces polycythemia by interfering with the respiratory function of vitamin C, hence stimulating erythropoiesis. In conclusion, the author points out that cobalt administered in small amounts over a long period will produce polycythemia without any other toxic effects.

BLOOD COAGULATION

Hemorrhagic Disorders Related to Prothrombin Deficiency.—Vitamin K and Prothrombin: Of the many functions and properties of the blood, that of coagulation is unique in being devoted primarily to the preservation of the blood itself. The several factors and their complex relationships concerned with the process of coagulation continue to engage the interest of chemists, physiologists and clinical investigators. Of the nature of such factors and the conditions which may predispose to or condition their aberration, greatest knowledge in recent years has been acquired with respect to prothrombin. Investigations dealing with prothrombin and with the role of vitamin K in its production have been devoted to varied aspects of the problem: chemical studies of natural and synthetic substances possessing vitamin K activity; the biologic assay of such materials and the standardization of methods of assay; procedures for the estimation of the effective prothrombin of whole blood or plasma; the experimental production and amelioration of vitamin K and prothrombin deficiencies; recognition of such deficiency states in man and the factors responsible for them, and, finally, adaptation of the information acquired by such studies to the correction of hemorrhagic disease or to lessening the risk of uncontrollable bleeding in man. We shall not attempt to discuss the contributions to the chemical knowledge of vitamin K made during the past year. For a complete review the reader is referred to the annotated bibliography of vitamin K published by Merck & Co., Inc.[139]

138. Davis, J. E.: The Effect of Ascorbic Acid Administration upon Experimental Polycythemia: The Mechanism of Cobalt Polycythemia, Am. J. Physiol. **129**:140, 1940.

139. Vitamin K: Annotated Bibliography, Rahway, N. J., Merck & Co., Inc., June 1940.

The results of a detailed study of the rate at which the plasma prothrombin level falls when newly hatched chicks are placed on a vitamin K–deficient diet are reported by Tidrick and associates.[140] They observed prolongation of the clotting time of whole blood when the prothrombin fell to about 30 per cent of the normal level for control chicks. Hemorrhages occurred at a level approximately 10 per cent of normal. Large doses of 2-methyl-1, 4-naphthoquinone [140a] corrected the deficit almost completely within six hours. Using chick methods of assay, Ansbacher [141] concluded that vitamin K_1 (2-methyl-3-phytyl-1, 4-naphthoquinone) and other phytyl derivatives of methylnaphthoquinone were not as active and not as readily utilized by the animal body as 2-methyl-1, 4-naphthoquinone. Ansbacher and his colleagues [142] also came to the conclusion that the water-soluble substances methylnaphthoquinone and methylnaphthohydroquinone are the most active vitamin K compounds known at present. Thayer and his associates,[143] using a six hour chick assay method, record the activity of 2-methyl-3-phytyl-1, 4-naphthoquinone as about one-half that of 2-methyl-1, 4-naphthoquinone and thereby disagree with the statements of Ansbacher that the difference in activity of the two compounds approximates 1 : 30. Richert and his associates [144] determined by bioassay methods the activity of various water-soluble antihemorrhagic compounds administered intravenously. On a molecular basis all were approximately equal to the standard, 2-methyl-1, 4-naphthoquinone, with the exception of dipotassium-1,4-dihydroxy-2-methylnaphthalene disulfate, which was distinctly less active.

A new method of preparing thromboplastin reagent from rabbit brain for the determination of prothrombin is described by Quick.[145] An acetone extract is dehydrated rapidly and the desiccated material placed in glass ampules from which the air is subsequently evacuated by means of an oil vacuum pump before the ampules are sealed in a flame.

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140. Tidrick, R. T.; Joyce, F. T., and Smith, H. P.: Vitamin K Deficiency and Prothrombin Levels: Effect of Vitamin K Administration, Proc. Soc. Exper. Biol. & Med. **42**:853, 1939.

140a. This compound has recently been given the name menadione.

141. Ansbacher, S.: Vitamin K, J. Biol. Chem. **133**:iii, 1940.

142. Ansbacher, S.; Fernholz, E., and Dolliver, M. A.: Water-Soluble Antihemorrhagic Compounds, Proc. Soc. Exper. Biol. & Med. **43**:652, 1940.

143. Thayer, S. A.; McKee, R. W.; Binkley, S. B., and Doisy, E. A.: Potencies of Vitamin K_1, and of 2-Methyl-1, 4-Naphthoquinone, Proc. Soc. Exper. Biol. & Med. **44**:585, 1940.

144. Richert, D.; Thayer, S. A.; McKee, R. W.; Binkley, S. B., and Doisy, E. A.: Bioassay of Water-Soluble Antihemorrhagic Compounds by Intravenous Administration, Proc. Soc. Exper. Biol. & Med. **44**:601, 1940.

145. Quick, A. J.: The Thromboplastin Reagent for the Determination of Prothrombin, Science **92**:113, 1940.

Dehydration of rabbit brain by acetone or by dioxane (diethylene dioxide) markedly increases the thromboplastic activity of the substance. In the sealed evacuated ampules the material apparently retains its potency indefinitely. Souter, Kark and Taylor [146] have employed "lyophilized" extract of dried whole rabbit brain, stored in evacuated containers, as a stable source of thromboplastin. These authors advocate the use of dried whole brain, rather than acetone-extracted brain, for thromboplastic activity, since the extreme potency of the latter material may prevent recognition of changes in prothrombin time until the content of prothrombin is considerably decreased.

A number of biologic materials other than tissue extracts exhibit thromboplastic activity. Among these are the venoms of certain snakes. Fullerton [147] has made successful use of venom from Russell's viper for this purpose. The procedure employed is identical with that of Quick except for the substitution of 0.1 cc. of the venom solution for rabbit brain extract. One-tenth milligram of the dried venom, available commercially, is dissolved in 1 cc. of distilled water. In the desiccated state the material retains its potency for several months.

Kaump and Greenwood [148] report that the Quick method for determination of prothrombin time gave best results in their hands when the constituents were used in the relative proportions of solution of calcium chloride 25 per cent, suspension of thromboplastin 25 per cent and plasma 50 per cent. The quantities employed were, respectively, 0.25, 0.25 and 0.5 cc. Of the extracts of various tissues tested none was superior to rabbit brain as a source of thromboplastin. Kato [149] has devised a modification of Quick's method using 10 cu. mm. of oxalated whole blood. The average normal value for the prothrombin time, by this procedure, is given as 20 ± 2 seconds. A one stage method utilizing serial dilutions of oxalated plasma, with the addition of thromboplastin in the form of beef lung extract, and solution of calcium chloride is described by Allen, Julian and Dragstedt.[150] They observed that a 35

146. Souter, A. W.; Kark, R., and Taylor, F. H. L.: A Stable Thromboplastin for Use in Quick's Prothrombin Test, Science **91**:532, 1940. Souter, A. W., and Kark, R.: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, Am. J. M. Sc. **200**:603, 1940.

147. Fullerton, H. W.: Estimation of Prothrombin: A Simplified Method, Lancet **2**:195, 1940.

148. Kaump, D. H., and Greenwood, J. H.: Plasma Prothrombin Determination, Am. J. Clin. Path. **10**:397, 1940.

149. Kato, K.: Microprothrombin Test with Capillary Whole Blood: Modification of Quick's Quantitative Method, Am. J. Clin. Path. **10**:147, 1940.

150. Allen, J. G.; Julian, O. C., and Dragstedt, L. R.: Use of Serial Dilutions in Determination of Prothrombin by the One Stage Technic, Arch. Surg. **41**:873 (Oct.) 1940.

per cent dilution of normal plasma was required before a change in the clotting time occurred. The dilution technic was found especially valuable in cases of delayed response to administration of vitamin K, such as may be shown by patients with nontropical sprue. In the plasma of a patient suffering with serum sickness a substance inhibiting the prothrombin-thrombin reaction was detected. Ziffren and co-workers [151] have published the details of a simple one stage method of measuring approximately the prothrombin content of whole blood. A modification of Howell's method for determination of prothrombin time is announced by Cheney.[152] Various amounts of solution of calcium chloride are mixed with oxalated plasma to which no thromboplastin has been added. A plasma dilution method for the estimation of prothrombin is reported by Thordarson.[153] Highly dilute oxalated plasma is added to a solution containing fibrinogen, thromboplastin, calcium and buffer salts. The clotting times of a range of dilutions of the patient's plasma are compared with those obtained with a standard prothrombin solution. The latter consists of the author's oxalated plasma, which is assumed to remain essentially unchanged with respect to prothrombin content. The method appears to have merit but is probably too time consuming to secure wide acceptance.

Warner and Flynn,[154] using the Warner, Brinkhous and Smith procedure for determination of prothrombin and employing rats suffering with a nutritional deficiency of vitamin K, observed that the addition of bile salts failed to modify appreciably the therapeutic efficacy of the water-soluble potassium salt of the disulfuric acid ester of 2-methyl-1,4-naphthoquinone. Elliott, Isaacs and Ivy [155] induced prothrombin deficiency in rats by the addition of 20 per cent by weight of liquid petrolatum to a diet which in other respects was similar to the diet of control animals. Vitamin K, administered subcutaneously, corrected the deficiency; supplementary vitamin D (viosterol in oil) was said to improve it, but the administration of vitamin A had no apparent effect.

151. Ziffren, S. E.; Owen, C. A.; Hoffman, G. R., and Smith, H. P.: A Simple Bedside Test for Control of Vitamin K Therapy, Am. J. Clin. Path. (Tech. Supp.) **4**:13, 1940.

152. Cheney, G.: The Plasma Coagulation Time as a Simple Test for Vitamin K Deficiency, Am. J. M. Sc. **200**:327, 1940.

153. Thordarson, O.: A Method for Quantitative Determination of Prothrombin in Plasma, Acta med. Scandinav. **104**:291, 1940.

154. Warner, E. D., and Flynn, J. E.: Absorption of Water-Soluble Vitamin K from Intestinal Tract, Proc. Soc. Exper. Biol. & Med. **44**:607, 1940.

155. Elliott, M. C.; Isaacs, B., and Ivy, A. C.: Production of "Prothrombin Deficiency" and Response to Vitamins A, D and K, Proc. Soc. Exper. Biol. & Med. **43**:240, 1940.

Prothrombin deficiency in rats was induced by Flynn and Warner [156] by means of biliary ligation and diet regulation. The potency of phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) and 2-methyl-1,4-naphthoquinone in correcting the condition was determined by intraperitoneal and by intravenous injection of these drugs.

Andrus, Lord and Kauer [157] observed that in dogs the level of the plasma prothrombin was lower in blood returning from the lungs than in that obtained from the arterial side of the pulmonary circulation. Differences in oxygen content of the blood were not responsible. The authors consider this difference evidence of pulmonary removal of prothrombin. Lord, Andrus and Moore,[158] using the Warner, Brinkhous and Smith technic for prothrombin estimation, determined by a curative assay method the vitamin K content of the livers of dogs subjected to various experimental procedures. They formulated a number of conclusions, based in part on their observations during the course of these studies. The authors state that in the formation of plasma prothrombin there enter an extrinsic factor (vitamin K), an intrinsic factor (bile salts), an absorptive mechanism (the intestinal epithelium) and an organ which stores vitamin K and elaborates plasma prothrombin (the liver). They draw an analogy between the mechanism involved in this process and that concerned with the formation of the erythrocyte-maturing factor. These authors reach the following conclusions: 1. Bile must reach the intestinal tract in order that absorption of fat-soluble vitamin K may occur, and the active constituents of the biliary secretion are the bile salts. 2. In dogs with obstructive jaundice or biliary fistula administration of bile salts alone does not suffice to prevent a fall in the plasma prothrombin. 3. Vitamin K is stored in the liver, and partial loss of the liver's supply is reflected in a linear manner by a corresponding decline in the prothrombin level. 4. The liver is the site of formation of plasma prothrombin, and for it to fulfil this function efficiently it must be healthy. 5. Prothrombin is constantly leaving the circulation, probably in the lungs. 6. The critical level of the plasma prothrombin with respect to hemorrhage is approximately 20 per cent of the normal value, as determined by the method employed.

Damage to the liver was caused in rats by poisoning with carbon tetrachloride, report Bollman, Butt and Snell.[159] The extent of hepatic

156. Flynn, J. E., and Warner, E. D.: Prothrombin Levels and Synthetic Vitamin K in Obstructive Jaundice of Rats, Proc. Soc. Exper. Biol. & Med. **43**:190, 1940.

157. Andrus, W. De W.; Lord, J. W., Jr., and Kauer, J. T.: Studies on the Fate of Plasma Prothrombin, Science **91**:48, 1940.

158. Lord, J. W., Jr.; Andrus, W. De W., and Moore, R. A.: Metabolism of Vitamin K and Role of the Liver in Production of Prothrombin in Animals, Arch. Surg. **41**:585 (Sept.) 1940.

159. Bollman, J. L.; Butt, H. R., and Snell, A. M.: The Influence of the Liver on the Utilization of Vitamin K, J. A. M. A. **115**:1087 (Sept. 28) 1940.

necrosis was greatest in animals fed a high fat diet and least in those with a high carbohydrate intake. Maximum regeneration occurred when a high protein diet was given. Hypoprothrombinemia developed in all the animals whose livers were damaged, and the level of the prothrombin could not be correlated with the type of diet received. The heparin content and the antithrombin activity of the plasma were not greatly affected by necrosis of the liver. No effect on the prothrombin levels of these experimental rats was observed after the administration of natural or synthetic vitamin K.

Injury to the liver was produced in dogs by Brinkhous and Warner [160] by the repeated administration of small doses of chloroform. The ensuing hypoprothrombinemia was not influenced by treatment with natural vitamin K and bile salts.

Kato and Poncher [161] point out that Whipple,[162] in 1912, recorded observations leading him to the conclusion that a deficiency of prothrombin was responsible for fatal hemorrhage in the newborn. By means of Kato's whole blood micromethod they determined the prothrombin time of 173 newborn infants. The subjects were classified as mature or premature on the basis of a body weight of 2,500 Gm. at birth. The average prothrombin time of 100 mature infants estimated on the day of birth was forty-three and two-tenths seconds, and the corresponding value for the premature babies was forty-six and five-tenths seconds, whereas the average normal adult prothrombin time determined by this method is twenty seconds. The authors found no correlation between the extent of prothrombin deficiency, as measured on the first day of life, and the degree of immaturity. They advocate prothrombin time determinations on the blood of all newborn infants or, as a safeguard, routine administration of vitamin K to all mothers before confinement.

Bray and Kelley,[163] using a micromodification of Quick's method, determined the prothrombin time on 17 samples of cord blood and on the blood of 23 newborn infants during the first week of life. The clotting time of cord blood was usually low, and the readings obtained during the first day of life were in the adult range of normal values.

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160. Brinkhous, K. M., and Warner, E. D.: Effect of Vitamin K on Hypoprothrombinemia of Experimental Liver Injury, Proc. Soc. Exper. Biol. & Med. **44**:609, 1940.

161. Kato, K., and Poncher, H. G.: The Prothrombin in the Blood of Newborn Mature and Immature Infants as Determined by the Microprothrombin Test, J. A. M. A. **114**:749 (March 2) 1940.

162. Whipple, G. H.: Hemorrhagic Disease: Septicemia, Melena Neonatorum and Hepatic Cirrhosis, Arch. Int. Med. **9**:365 (March) 1912; Hemorrhagic Disease: Antithrombin and Prothrombin Factors, ibid. **12**:637 (Dec.) 1913.

163. Bray, W. E., and Kelley, O. R.: Prothrombin Studies, Especially in the Newborn, Am. J. Clin. Path. **10**:154, 1940.

Thereafter the time increased to a maximum between the second and the fifth day and subsequently fell. The time was greatly prolonged in cases of hemorrhagic disease of the newborn. No correlation was found between the platelet count and the prothrombin level of the blood. Quick and Grossman [164] also observed normal prothrombin times at birth, with an abrupt increase during the first few days of life and subsequent spontaneous and prompt restoration of normal values. Absence of intestinal bacteria was considered responsible for vitamin K deficiency and the consequent fall in the prothrombin content of the plasma. They attributed hemorrhagic disease of the newborn to delayed restoration of the prothrombin level, a process which could be hastened by the oral administration of vitamin K. Salomonsen [165] likewise ascribes the hypoprothrombinemia of infancy to vitamin K deficiency dependent on a relatively sterile intestinal tract. He found that the administration of a little cow's milk periodically from the second hour of life prevented later disturbances of blood coagulation. Tocantins [166] observed a case of congenital atresia of the duodenum, with icterus and hemorrhagic manifestations, in a mulatto infant. Although the termination was fatal, the prothrombin time returned to normal spontaneously, and the bleeding ceased as the jaundice disappeared. Consequently, the author discards the theory attributing low prothrombin levels in infancy to lack of bacterial activity and suggests that the hypoprothrombinemia is due to incapacitation of the liver resulting from an excessive load of pigment from the breakdown of hemoglobin. An additional factor, he states, may be the abrupt termination of a supply of prothrombin from the placenta.

Nygaard [167] considers that inactivity of intestinal flora is but one factor in the causation of the transitory hypoprothrombinemia of the newborn and advises routine administration of vitamin K to women for a period of two weeks before expected confinement. He has used 2-methyl-1,4-naphthoquinone in a daily dose of 10 mg. Koller and Fiechter [168] found that giving vitamin K by mouth or by intramuscular

164. Quick, A. J., and Grossman, A. M.: The Nature of the Hemorrhagic Disease of the Newborn: Delayed Restoration of the Prothrombin Time, Am. J. M. Sc. **199**:1, 1940.

165. Salomonsen, L.: Hemorrhagic Disease of Newborn, Due to Hypoprothrombinemia, Nord. med. **7**:1309, 1940.

166. Tocantins, L. M.: Probable Mechanism of the "Physiologic" Hypoprothrombinemia of the Newborn, Am. J. Dis. Child. **59**:1054 (May) 1940.

167. Nygaard, K. K.: Prothrombin Deficiency as Cause of Hemorrhagic Diathesis in the Newborn: Prophylaxis and Therapy with Vitamin K, Nord. med. (Norsk. mag. f. lægevidensk) **7**:1535, 1940.

168. Koller, F., and Fiechter, N.: Die hämorrhagische Diathese des Neugeborenen und ihre Beziehung zum Vitamin K, Schweiz. med. Wchnschr. **70**:136, 1940.

injection from the first day of life prevented the rise in prothrombin time which occurs usually between the second and the sixth day. Case reports and analyses of plasma prothrombin values are given by Dam and his associates.[169] In normal infants they found that a moderate vitamin K deficiency associated with hypoprothrombinemia develops during the first few days of life. Marked decrease of prothrombin was observed in cases falling under the clinical triad of hydrops foetalis, icterus gravis neonatorum and congenital anemia of the newborn. Increases in the plasma prothrombin content were demonstrated in 2 infants suffering with icterus gravis. Aside from its hemostatic effect, the use of vitamin K failed to influence the anemia.

The effects on the plasma prothrombin of infants exerted by various synthetic vitamin K compounds administered to the mother in labor were studied by Hellman, Moore and Shettles.[170] Waddell, Guerry and Birdsong [171] were able to prevent the development of hypoprothrombinemia in newborn infants by administration either of natural vitamin K orally during the first few days of life or of natural or synthetic vitamin K to the mother throughout the last two weeks of gestation. Snelling,[172] using Quick's method, observed that the prothrombin time of cord blood was prolonged in many newborn infants, without associated evidence of hemorrhage. The daily administration of natural or synthetic vitamin K to prospective mothers had no effect on the maternal prothrombin time but shortened the time of coagulation of cord blood. He recommends the antepartum use of vitamin K in the prophylaxis of hemorrhagic disease of the newborn. Since orally administered vitamin K may not be retained or absorbed, the parenteral route is often preferable. Snelling reports that the intravenous use of 2-methyl-1,4-naphthoquinone lowers the prothrombin time of infants and is followed by cessation of bleeding in cases of hemorrhagic disease. The usual dose is 0.5 to 1.0 mg. in a fresh solution, not over one week old, and toxic effects have not been observed. The author recommends transfusion as a supplementary therapeutic measure in treating patients with low hemoglobin values.

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169. Dam, H.; Tage-Hansen, E., and Plum, P.: Vitamin-K Lack in Normal and Sick Infants, Lancet **2**:1157, 1939.

170. Hellman, L. M.; Moore, W. T., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in the New Born Infant: III. A Study of the Vitamin K Activity of Various Naphthohydroquinone Derivatives, Bull. Johns Hopkins Hosp. **66**:379, 1940.

171. Waddell, W. W., Jr.; Guerry, Du P., III, and Birdsong, M.: The Role of Vitamin K in the Etiology, Prevention and Treatment of Hypoprothrombinemia and the Hemorrhagic Diathesis of the Newborn, South. M. J. **33**:974, 1940.

172. Snelling, C. E.: Vitamin K in Hemorrhagic Disease of the Newborn Infant, J. Pediat. **17**:615, 1940.

Low plasma prothrombin levels were found in 52 of 76 infants examined during the first eight days of life by Kove and Siegel.[173] The average value was lowest during the first two days. Diet histories obtained from the mothers of 68 of the babies failed to reveal any correlation between the maternal dietary intake of vitamin K and the prothrombin values for the infants. However, such a correlation was established when medicinal vitamin K was taken by the mother before confinement. The authors advise routine antepartum administration of the vitamin. Waddell and Lawson [174] present evidence indicating that avitaminosis K and associated prothrombin deficiency may be an important factor in many cases of intracranial hemorrhage occurring during birth. The antepartum use of vitamin K is believed to be of value in preventing such accidents. The authors give the vitamin to all women before delivery, as well as to all infants during the first days of life. General discussions of vitamin K and hypoprothrombinemia with reference to pediatrics have been published by Grossman [175] and by Thompson.[176]

The prothrombin content of the plasma during pregnancy has been studied by Thordarson.[177] The level, he found, begins to increase at the third month of gestation and continues to rise until delivery. The prothrombin content of blood from normal nonpregnant women was expressed by an index of 100; in pregnant women at three months average values ranged between 111 and 123 and at six months between 146 and 149, while at nine months the average value was 169. Beginning on Sept. 1, 1939, Hellman, Shettles and Eastman [178] gave orally 2 mg. of 2-methyl-1,4-naphthoquinone to every other patient admitted in labor to the Johns Hopkins Hospital. In the control series of 392 subjects 16, or 4.1 per cent, of the deliveries resulted in stillbirths or neonatal deaths. The corresponding figure for the treated series, comprising 384 members, was 6, or 1.5 per cent. The probability is 6:1 against the difference being due to an error in sampling. According to the authors, review

173. Kove, S., and Siegel, H.: Prothrombin in the Newborn Infant: Relationship to the Maternal Dietary Vitamin K Intake, J. Pediat. **17**:448, 1940.

174. Waddell, W. W., Jr., and Lawson, G. M.: Hemorrhagic Diathesis of the Newborn: Further Observations Concerning Prevention and Treatment, J. A. M. A. **115**:1416 (Oct. 26) 1940.

175. Grossman, A. M.: Vitamin K for the Pediatrician with Special Reference to Physiologic Hypoprothrombinemia of Newborn Infants, J. Pediat. **16**:239, 1940.

176. Thompson, W. H.: Prothrombin Deficiency and Vitamin K in the Newborn Period, J. Tennessee M. A. **33**:218, 1940.

177. Thordarson, O.: Hyperprothrombinaemia During Pregnancy, Nature, London **145**:305, 1940.

178. Hellman, L. M.; Shettles, L. B., and Eastman, N. J.: Vitamin K in Obstetrics: A Review of One Year's Experience, Am. J. Obst. & Gynec. **40**:844, 1940.

of the necropsy observations attaches still greater significance to the results. They recommend the routine antepartum administration of vitamin K. Fitzgerald and Webster [179] studied the effects of vitamin K given during labor. More than 100 women, including treated subjects and controls, were observed. No change in the maternal plasma prothrombin time occurred in patients who did not receive vitamin K. Administration during a period of one to twenty-four hours before delivery of either natural vitamin K by mouth or of 2 mg. of 2-methyl-1,4-naphthoquinone by the intravenous route was followed by a rise in the prothrombin content of both the maternal and the cord blood. These workers observed a definite depression of the prothrombin level in both mother and child after the use of pentobarbital sodium as an analgesic during labor.

According to Weir, Butt and Snell,[180] factors important in the development of hypoprothrombinemia are inadequate intake of vitamin K or the substances necessary for its manufacture in the intestine, impairment of absorption of the vitamin and hepatic injury. Intravenous use of four synthetic compounds in clinical cases of hypoprothrombinemia were attended with excellent results, except in patients with disease of the liver. The intravenous method of administration possesses the advantages of precise dosage, instant availability and elimination of the variable factor of absorptive capacity. The rapidity of action of the drug suggested to the authors that it may function in an enzymatic manner.

The Ivy method for determination of bleeding time and the serum volume test of Boyce and McFetridge, with correction for anemia, were used by Ferguson and his associates [181] for the estimation of the bleeding time in cases of jaundice. They report that either of these tests, or the combined application of the two, revealed the presence of a hemorrhagic tendency in every case of jaundice in which such a tendency was indicated by the results of the Quick method for determination of prothrombin time. Wilson [182] determined the level of the plasma prothrombin in 41 patients without obstructive jaundice or biliary fistula and found a correlation between the values obtained and the results of the hippuric acid test of hepatic function. Clinical conditions

179. Fitzgerald, J. E., and Webster, A.: Effect of Vitamin K Administered to Patients in Labor, Am. J. Obst. & Gynec. **40**:413, 1940.

180. Weir, J. F.; Butt, H. R., and Snell, A. M.: Further Observations on the Clinical Use of Vitamin K, Am. J. Digest. Dis. **7**:485, 1940.

181. Ferguson, L. H.; Calder, D. G., Jr., and Reinhold, J. G.: The Ivy Bleeding Time: Serum Volume Index and Prothrombin Content of Blood in Estimating Bleeding Tendency in Jaundice, Surg., Gynec. & Obst. **71**:603, 1940.

182. Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Human Subjects, J. Lab. & Clin. Med. **25**:1139, 1940.

studied included cirrhosis of the liver and various disorders of the blood. No correlation between the fibrinogen content of the plasma and the ability to synthesize and excrete hippuric acid was observed. The galactose tolerance test gave normal results for all of the subjects examined, whereas the degree of bromsulphalein retention varied widely. Cullen and his co-workers [183] report on a clinical study of changes of the plasma prothrombin level following anesthesia induced by various agents. Lowering of the prothrombin content followed administration of chloroform, whereas neither ether nor cyclopropane produced such an effect.

The existence of avitaminosis K and associated hypoprothrombinemia on an exclusive nutritional basis is still in controversy, but evidence is accumulating that dietary deficiency must be regarded at least as an important contributing factor in some cases of lowered plasma prothrombin. Eighteen cases in which there were associated clinical signs of various forms of avitaminosis, other than K, are reported by Scarborough.[184] In none of these was prolongation of prothrombin time exhibited by the method of Quick. His results are at variance with those published by Kark and Lozner.[185] They observed 4 patients, with evidence of avitaminosis and a history of dietary deficiency, in whom the prothrombin coagulation time was delayed. Hemorrhagic manifestations in these patients were attributed to lack of vitamin C rather than of vitamin K, but the prothrombin times were restored to normal after oral administration of vitamin K. None of the patients was jaundiced. Mackie [186] reports the results of prothrombin studies and the response to treatment of 277 patients with various disorders. Of these, 57 exhibited hypoprothrombinemia, by Quick's method, in the absence of jundice or evidence of disease of the liver. Some patients improved with diet therapy alone; others responded to oral use of vitamin K without bile salts; one group was treated successfully with dehydroxycholic acid (obtainable as decholin) without vitamin K, and some patients required the two therapeutic agents in combination. Six members of the series exhibited severe hemorrhagic manifestations, and among these either absorptive difficulty or disease of the liver, rather

183. Cullen, S. C.; Ziffren, S. E.; Gibson, R. B., and Smith, H. P.: Anesthesia and Liver Injury, with Special Reference to Plasma Prothrombin Levels, J. A. M. A. **115**:991 (Sept. 21) 1940.

184. Scarborough, H.: Nutritional Deficiency of Vitamin K in Man, Lancet **1**:1080, 1940.

185. Kark, R., and Lozner, E. L.: Nutritional Deficiency of Vitamin K in Man: A Study of Four Non-Jaundiced Patients with Dietary Deficiency, Lancet **2**:1162, 1939.

186. Mackie, T. T.: Vitamin K Deficiency in the Absence of Jaundice, New York State J. Med. **40**:987, 1940.

than dietary deficiency, was regarded as a chief cause of hypoprothrombinemia. Mason [187] observed normal plasma prothrombin levels in patients suffering with pernicious anemia, pellagra or sprue who were receiving treatment with liver extract and vitamins.

The response of patients exhibiting lowered values for plasma prothrombin in association with biliary and hepatic disease to treatment with natural and synthetic vitamin K given by oral, intramuscular and parenteral routes has been the subject of numerous communications. It has been generally observed that vitamin K therapy is inefficacious in cases of severe hepatic disease, and at present this constitutes the only recognized condition in which the intravenous administration of potent synthetic vitamin K compounds is without effect. Several authors [188] comment on the information regarding hepatic function which may be afforded by a determination of prothrombin time and the degree of response to parenteral administration of vitamin K.

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187. Mason, H. C.: Normal and Abnormal Prothrombin Levels, Proc. Soc. Exper. Biol. & Med. **44**:70, 1940.

188. Andrus, W. De W., and Lord, J. W., Jr.: Clinical Investigations of Some Factors Causing Prothrombin Deficiencies: Significance of the Liver in Their Production and Correction, Arch. Surg. **41**:596 (Sept.) 1940; Use of Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in Treatment of Prothrombin Deficiencies, with Note on Role of Liver in Response to This and Other Substances with Vitamin K Activity, Ann. Surg. **112**:783, 1940. Pohle, F. J., and Stewart, J. K.: Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, J. Clin. Investigation **19**:365, 1940. Allen, J. G., and Julian, O. C.: Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, Arch. Surg. **41**:1363 (Dec.) 1940. Cheney, G.: Vitamin K Deficiency in a Case of Gall Bladder Disease Without Clinical Jaundice or Hepatitis, Am. J. Digest. Dis. **7**:521, 1940. Townsend, S. R., and Mills, E. S.: Haemorrhagic Tendency Associated with Prothrombin Deficiency and Its Treatment with Vitamin K and Bile, Canad. M. A. J. **42**:541, 1940. Rhoads, J. E., and Fliegelman, M. T.: The Use of 2-Methyl-1, 4-Naphthoquinone (a Synthetic Vitamin K Substitute) in the Treatment of Prothrombin Deficiency in Patients, J. A. M. A. **114**:400 (Feb. 3) 1940. Aggeler, P. M.; Lucia, S. P., and Goldman, L.: Effect of Synthetic Vitamin K Compounds on Prothrombin Concentration in Man, Proc. Soc. Exper Biol. & Med. **43**:689, 1940. Macfie, J. M.; Bacharach, A. L., and Chance, M. R. A.: The Vitamin K Activity of 2-Methyl-1, 4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice, Brit. M. J. **2**:1220, 1939. Butt, H. R.; Snell, A. M.; Osterberg, A. E., and Bollman, J. L.: Treatment of Hypoprothrombinemia: Use of Various Synthetic Compounds Exhibiting Anti-Hemorrhagic Activity (Vitamin K_1 Activity), Proc. Staff Meet., Mayo Clin. **15**:69, 1940. Andrus, W. De W., and Lord, J. W., Jr.: Correction of Prothrombin Deficiencies by Means of 2-Methyl-1, 4-Naphthoquinone Injected Intramuscularly, J. A. M. A. **114**:1336 (April 6) 1940. Kark, R., and Souter, A. W.: Synthetic Vitamin K in the Treatment of Hypoprothrombinaemia, Lancet **1**:1149, 1940. Norcross, J. W., and McFarland, M. D.: Intravenous Use of 2-Methyl-1, 4-Naphthoquinone in Hypoprothrombinemia: Clinical Observations, J. A. M. A. **115**:2156 (Dec. 21) 1940.

Because of the increasing use of "banked" blood for transfusions, interest has been shown in the effects of storage on the prothrombin content of such blood. Quick [189] observed a significant decrease in prothrombin occurring within two days of removal of blood. Reinhold, Valentine and Ferguson [190] report that 73 per cent or more of the original prothrombin content of stored blood is present up to three days; after seven days of storage the majority of samples of blood possess less than half of their original prothrombin. Warner, DeGowin and Seegers [191] noted a gradual decrease in the prothrombin content of preserved blood, amounting to about 50 per cent of the original level after three weeks of storage. However, they found that at the end of ten days most blood retained 90 per cent of its prothrombin activity. The use of either a solution of citrate alone or a solution of dextrose and citrate as an anticoagulant and preserving agent made no difference in the rate of prothrombin loss. Ziegler, Osterberg and Hovig [192] report a 60 per cent loss of prothrombin content after three weeks of storage, but only a 10 to 20 per cent decrease after eight days.

Several general articles on the role of vitamin K and prothrombin in hemorrhagic disorders have appeared in the past year.[193] An extensive and detailed review of the entire subject, embodying the literature which appeared up to and including 1939, has been published by Brinkhous.[194]

Factors in Blood Coagulation Other Than Vitamin K and Prothrombin.—A résumé and recapitulation of his observations and views on the mechanism of blood clotting have been pubished by Ferguson.[195] According to this author, coagulation is explained in part by the formation of an intermediary colloidal complex containing prothrombin, cephalin and calcium in definite quantitative proportions. "Ripe"

189. Quick, A. J.: Prothrombin in Preserved Blood, J. A. M. A. **114**:1342 (April 6) 1940.

190. Reinhold, J. G.; Valentine, E. H., and Ferguson, L. K.: The Effect of Storage on the Prothrombin Content of Citrated Blood, Am. J. M. Sc. **199**:774, 1940.

191. Warner, E. D.; DeGowin, E. L., and Seegers, W. H.: Studies on Preserved Human Blood: Decrease in Prothrombin Titer During Storage, Proc. Soc. Exper. Biol. & Med. **43**:251, 1940.

192. Ziegler, E. R.; Osterberg, A. E., and Hovig, M.: The Prothrombin Changes in Banked Blood, J. A. M. A. **114**:1341 (April 6) 1940.

193. Larson, C. P.: The Present Status of Vitamin K, West. J. Surg. **48**:352, 1940. Greer, A. E.: The Place of Vitamin K in Hemorrhagic Diseases, Texas State J. Med. **36**:218, 1940. Vitamin K and Cholemic Bleeding, editorial, J. A. M. A. **116**:143 (Jan. 11) 1941.

194. Brinkhous, K. M.: Plasma Prothrombin: Vitamin K, Medicine **19**:329, 1940.

195. Ferguson, J. H.: The Role of Blood Clotting Anomalies in the Hemorrhagic Diseases, J. Lab. & Clin. Med. **26**:52, 1940.

thrombin can be prepared free from calcium. Prolongation of the clotting time may contribute to the development of those hemorrhagic states in which there can be demonstrated or postulated either deficiency of thromboplastin or prothrombin or excess of antithrombic factors. Calcium, according to Ferguson, may be excluded from practical consideration. Factors such as fibrinogen and platelet defects play their part in determining the effectiveness of coagulation and thrombosis in the arrest of hemorrhage. These, he considers, are all controlling or immediate mechanisms, and the prior causative factors, including capillary injury, must also receive consideration.

Views on the clotting mechanism in some respects at variance with those of Ferguson are expressed by Quick.[196] He believes that calcium is already bound to prothrombin before its reaction with thromboplastin and that ionized calcium takes no part in the transformation of prothrombin to thrombin. The prothrombin-calcium combination, in Quick's opinion, is identical with Ferguson's intermediary complex. His conclusions are based, in part, on results of experiments with chicken blood, without the use of anticoagulant but with an excess of thromboplastin. The studies were so designed that calcium would be the only variable factor present.

Based on the coagulation theory first expounded by Morawitz in 1908, and later developed by Howell, Quick[197] has published a clinical classification of hemorrhagic diseases. Other general discussions of disturbances of blood coagulation and their clinical manifestation are given by Heck[198] and Sanford.[199]

Inactivation of the thrombin of beef plasma by treatment with human or beef plasma or horse serum is reported by Stewart and Rourke.[200] The thrombin was not inactivated by a solution of fibrinogen. A component of the albumin fraction of the plasma is believed responsible for the inactivating effect. A method is described by Wilson[201] for the quantitative determination of the antithrombic activity of serum and plasma, and the unit of antithrombin is defined as that amount which

196. Quick, A. J.: Calcium in the Coagulation of the Blood, Am. J. Physiol. **131**:455, 1940.

197. Quick, A. J.: Classification of Hemorrhagic Diseases Due to Defects in the Coagulation Mechanism of the Blood, Based on Recently Published Studies, Am. J. M. Sc. **199**:118, 1940.

198. Heck, F. J.: The Differential Diagnosis of Diseases with Hemorrhagic Manifestations, Texas State J. Med. **36**:536, 1940.

199. Sanford, H. M.: Studies in Blood Coagulation Disturbances, J. Missouri M. A. **37**:409, 1940.

200. Stewart, J. D., and Rourke, G. M.: On the Inactivation of Thrombin by Plasma Protein, J. Clin. Investigation **19**:695, 1940.

201. Wilson, S. J.: Quantitative Studies on Antithrombin, Proc. Soc. Exper. Biol. & Med. **43**:676, 1940.

will inactivate or neutralize 1 unit of thrombin during four minutes' incubation at 28 C. Solandt and Best [202] report studies on the influence of heparin on the coagulation mechanism and state that a single dose of heparin sufficient to raise the clotting time of the blood of an anesthetized dog to over six hours did not prevent the agglutination of platelets in the presence of a maximal stimulus. With larger doses of heparin the effect on platelet agglutination, unlike that on the clotting time, took fifteen to fifty minutes to develop.

Seventeen commercially available products with claimed thromboplastic activity and ten solutions of thromboplastin obtained from various species were tested by Aggeler and Lucia [203] for their influence on coagulation of plasma from normal human subjects and plasma from subjects with hemophilia. Commercial preparations designed for parenteral use exhibited no effect on the clotting times of the plasma tested. Only products suitable for local or oral use were found to possess activity.

Lozner, Jolliffe and Taylor [204] report the case of a Negro with generalized tuberculous lymphadenitis and prolonged coagulation time. The clotting defect was not like that present in persons with hemophilia, and anticoagulant activity toward normal blood was demonstrated in the patient's plasma.

Forty-four patients in whom hematemesis or melena had occurred, for the most part associated with peptic ulcer, were studied by Moss, Schiff, Stevens and Rich.[205] Ascorbic acid levels of the plasma were determined and frequently were found to be low in cases of ulcer, although no etiologic significance with respect to hemorrhage was attached to this observation. It was found that the bleeding time, estimated by the Ivy method, may be prolonged and reduction of the level of serum calcium may occur in association with hematemesis from a variety of causes. In these cases there was no prolongation of the prothrombin time and the bleeding time, determined by the Duke method, the fibrinogen content of the blood and the number of platelets were normal. Examination of the sternal marrow revealed no abnormality other than active regeneration.

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202. Solandt, D. Y., and Best, C. H.: Time-Relations of Heparin Action on Blood-Clotting and Platelet Agglutination, Lancet **1**:1042, 1940.

203. Aggeler, P. M., and Lucia, S. P.: The Potency of Blood Coagulating Substances: Biologic Assay, Am. J. M. Sc. **199**:181, 1940.

204. Lozner, E. L.; Jolliffe, L. S., and Taylor, F. H. L.: Hemorrhagic Diathesis with Prolonged Coagulation Time Associated with a Circulating Anticoagulant, Am. J. M. Sc. **199**:318, 1940.

205. Moss, H. K.; Schiff, L.; Stevens, R. J., and Rich, M. L.: The Blood in Cases of Hematemesis and Melena with Reference to Factors Influencing Hemorrhage, Am. J. Digest. Dis. **7**:490, 1940.

Calder and Kerby [206] found nicotinic acid to be effective in promoting coagulation in patients suffering with brucellosis. They also observed its value in correcting clotting and bleeding defects in other toxic and infectious conditions. The effect of nicotinic acid was not identifiable with the action of calcium, thromboplastic material from platelets, prothrombin or thrombin. Experiments in vitro indicate that it may exert a neutralizing effect on antithrombin.

Extracts of shepherd's-purse and certain other plants were found by Steinberg, Segal and Parris [207] to possess blood-coagulating activity. The oxalic acid content of the extracts was apparently largely responsible for their effect. The material was administered by intramuscular and intravenous injection in an effort to control hemorrhagic tendencies. The authors devised a "clotting unit" for the substance employed and obtained a large measure of success from its use in many apparently unrelated hemorrhagic disorders.

An experimental and clinical study of the effects of induced fever in promoting hemorrhage is reported by Wilson and Doan.[208] They observed that elevation of body temperature results in anoxia and in depletion of the liver glycogen, which leads to hepatic and megakaryocytic injury, with consequent decrease in the prothrombin content of the plasma and the number of platelets in the blood. A reduction of fibrinogen may also occur. The changes were reversible.

Hemorrhagic Disorders Other Than Those Related to Prothrombin Deficiency.—Essential Thrombopenic Purpura: No important contributions have been made toward the solution of the problem of the mechanism of platelet deficiency and disturbed capillary integrity in essential purpura. Wiseman, Doan and Wilson,[209] in a general article on this disorder, accompanied by case reports, favor excessive thrombocytolysis by an overactive spleen as the most probable cause of thrombopenia. They find no evidence of qualitative change in the megakaryocytes of the marrow. The authors recommend an attempt to sustain patients with this disease by medical measures, if possible, until a remission of activity occurs, but advocate splenectomy as a method of permanent cure in most cases. In their opinion, the more pronounced the bleeding the more urgent are the indications for removal of the spleen. An opposing view

206. Calder, R. M., and Kerby, G. P.: The Effect of Nicotinic Acid on Blood Coagulation, Am. J. M. Sc. **200**:590, 1940.

207. Steinberg, A.; Segal, H. I., and Parris, H. M.: Role of Oxalic Acid and Certain Related Dicarboxylic Acids in Treatment and Control of Hemorrhage, Ann. Otol., Rhin. & Laryng. **49**:1008, 1940.

208. Wilson, S. J., and Doan, C. A.: The Pathogenesis of Hemorrhage in Artificially Induced Fever, Ann. Int. Med. **13**:1214, 1940.

209. Wiseman, B. K.; Doan, C. A., and Wilson, S. J.: The Present Status of Thrombocytopenic Purpura, with Special Reference to Diagnosis and Treatment, J. A. M. A. **115**:8 (July 6) 1940.

regarding the mechanism of platelet decrease in essential purpura is expressed by Limarzi and Schleicher.[210] They report studies of the peripheral blood and sternal marrow made on 29 subjects, including 5 normal men, 5 normal women and 7 patients with thrombopenic purpura, in 2 of whom the condition was chronic. The megakaryocytes of normal marrow are classified as young, adult and degenerated forms, on the basis of cytoplasmic changes with azure granulation. Megakaryocytes observed in cases of essential purpura were almost all young, owing, the authors believe, to inhibition of normal maturation. The platelets, they found, were reduced equally in the bone marrow and in the peripheral blood. According to these investigators, the beneficial effect of splenectomy lies in the elimination of the inhibitory action on the development of megakaryocytes, thus enabling the bone marrow to revert to normal conditions. Observations somewhat at variance with those of Limarzi and Schleicher but leading to essentially the same conclusions are reported by Revol.[211] Examinations of the material obtained by a series of sternal marrow aspirations performed before and after splenectomy on a patient suffering with thrombopenic purpura indicated a failure of release of platelets by the megakaryocytes. Morphologically these giant cells appeared to be mature and identical with those present in normal marrow, but, until the spleen was removed, they failed to break up into thrombocytes. The author postulates an inhibitory action of the spleen on platelet release. Greiner [212] reports a case of essential purpura in which the platelet count was low during hemorrhagic episodes, but the number could not be correlated with the bleeding time. A correlation was, however, established between the level of the platelets and the degree of clot retraction. After severe hemorrhages morphologic changes in the thrombocytes were noted, with the appearance of large, irregular and deeply stained forms. In this case tests showed that capillary resistance was normal. No treatment offered more than transient benefit. Splenectomy was performed, with subsequent cessation of bleeding, but after nine and one-half months relapse occurred.

The onset of thrombopenic purpura at puberty or shortly thereafter has been noted by many observers. Two such occurrences are reported by Goldburgh and Gouley,[213] who mention other instances described

210. Limarzi, L. R., and Schleicher, E. M.: The Reaction of Peripheral Blood and Bone Marrow in Chronic Hemorrhage and in Essential Thrombopenic Purpura, J. A. M. A. **114**:12 (Jan. 6) 1940.

211. Revol, L.: Etude du myélogramme dans un cas de purpura hémorragique avec thrombopénie; modifications à la suite de la splénectomie, Sang **13**:884, 1939.

212. Greiner, K.: Zur Klinik und Therapie der essentiellen Thrombopenie, Ann. pædiat. **154**:265, 1940.

213. Goldburgh, H. L., and Gouley, B. A.: Postpubertal Menorrhagia and Its Possible Relations to Thrombocytopenic Purpura Haemorrhagica, Am. J. M. Sc. **200**:499, 1940.

in the literature. According to these authors, evidences of abnormal coagulation develop gradually, and excessive loss of menstrual blood may precede by many months detectable platelet deficiency, prolonged bleeding time, increased capillary permeability and spontaneous purpuric manifestations. It is suggested that abnormalities of the menstrual cycle, perhaps concerned with the corpus luteum, may lead to stimulation of the thrombocytolytic activity of the spleen. Snaith [214] reports the case of a married woman of 27 in whom menorrhagia was the only hemorrhagic symptom associated with thrombopenia. Recovery followed splenectomy.

An interesting observation on the control of bleeding in patients afflicted with thrombopenic purpura is described by Tzanck, Sureau and Dreyfuss.[215] They found transfusions of fresh blood and intravenous injections of platelet extracts valueless for this purpose. However, in 3 cases hemorrhage ceased after the administration of blood which had been stored for ten days. The phenomenon was ascribed to a combination of circumstances, including the presence in the blood of products of platelet disintegration and active ferments, lowering of the alkalinity of the plasma and increase in lactic acid content. After fifteen days of storage the blood no longer possessed ferment activity and was ineffective in the control of bleeding.

Intracranial hemorrhage occurs not infrequently in the course of thrombopenic purpura and is responsible for the death of many patients with this disorder. However, as the first evidence of hemorrhagic proclivity it is exceedingly rare. A case is reported by Gitt and Weiss.[216] A youth aged 18 suffered an abrupt onset of symptoms associated with bloody spinal fluid, retinal hemorrhages and hematemesis. An apparent cure followed removal of the spleen.

Further evidence of the possible beneficial effects of solution of parathyroid administered to patients suffering with thrombopenic purpura is announced by Levine and Michelson.[217] A 12 year old girl was given a total of 400 units of solution of parathyroid after splenectomy had failed to induce remission. Symptomatic improvement ensued, but the platelet level remained low, and two months after removal of the

214. Snaith, L.: Menorrhagia Due to Essential Thrombocytopenia, Lancet **2**:684, 1940.

215. Tzanck, A.; Sureau, M., and Dreyfuss, A.: Trois cas de thrombopénie aiguë. Arrêt des hémorrhagies par transfusion de sang conservé âgé de 10 jours, Sang **13**:996, 1939.

216. Gitt, J. J., and Weiss, E. J.: Subarachnoid Hemorrhage as a Primary Manifestation of Thrombocytopenic Purpura; Splenectomy and Recovery, J. Missouri M. A. **37**:73, 1940.

217. Levine, D. B., and Michelson, H.: Acute Thrombopenic Purpura Treated Successfully with Solution of Parathyroid, J. A. M. A. **115**:360 (Aug. 3) 1940.

spleen the thrombocytes numbered 75,000 per cubic millimeter. Aspiration of sternal marrow two weeks after splenectomy revealed little evidence of megakaryocyte maturation. Remission continued during an eleven month period of observation.

According to Priestley,[218] a woman aged 20 underwent splenectomy for thrombopenic purpura, and during convalescence typical infectious mononucleosis developed.

The case of a 2 month old boy with an extensive benign capillary hemangioma and associated thrombopenic purpura is reported by Kasabach and Merritt.[219] The hemangioma responded to roentgen therapy, and the purpura disappeared spontaneously.

Interest continues in the effect of splenic extracts on the platelet level of rabbit blood. Hodge and Strong [220] prepared acetone extracts of the spleens of 2 patients suffering with thrombopenic purpura and observed no effects on the numbers of erythrocytes and platelets or the bleeding and clotting times of the blood of rabbits to which the material was administered. On the other hand, one of the few qualifiedly favorable reports on the platelet-reducing action of such extracts has been published by Hobson and Witts.[221] When relatively large doses were used it was found that the acetone extract of spleen obtained from a patient suffering with essential purpura was more effective than an extract prepared from the spleen of a healthy person in reducing the number of platelets in rabbit's blood. These authors also observed that an emulsion of normal spleen in Ringer's solution was more active than an acetone extract of the same material in bringing about decrease of thrombocytes in rabbits.

Secondary Thrombopenic Purpura: Among the toxic effects of the arsphenamines and related compounds on the blood-forming organs, thrombopenic purpura is of especial interest because of its sudden onset, its usually short duration, its association with increased capillary permeability and the lack of evidence of involvement of marrow elements other than platelets. This condition is to be distinguished from the general and prolonged myeloid hypoplasia, including involvement of the platelet-forming elements, which may also follow administration of arsphenamine. A number of reports of clinical and experimental inves-

218. Priestley, J. H.: Thrombocytopenic Purpura Treated by Splenectomy and Complicated by Infectious Mononucleosis, M. J. Australia **1**:898, 1940.

219. Kasabach, H. H., and Merritt, K. K.: Capillary Hemangioma with Extensive Purpura: Report of a Case, Am. J. Dis. Child. **59**:1063 (May) 1940.

220. Hodge, I. G., and Strong, P. T.: The Effect of Splenic Extracts of Patients with Thrombocytopenic Purpura on the Platelet Count of Rabbits, Bull. Ayer. Clin. Lab., Pennsylvania Hosp. **3**:267, 1939.

221. Hobson, F. C. G., and Witts, L. J.: Platelet-Reducing Extracts of the Spleen, Brit. M. J. **1**:50, 1940.

tigation have indicated that low ascorbic acid content of the blood and tissues may be associated with increased susceptibility to the toxic effects of the arsenicals used in the treatment of syphilis, but there has been no unanimity of opinion on the subject. The literature dealing with this question has been reviewed by Falconer, Epstein and Mills.[222] They report clinical studies made on 6 patients known to be sensitive to neoarsphenamine and 1 sensitive to bismarsen. It was not possible to standardize the sensitivity reactions of these patients in terms of the size of the dose of the drug to which they were sensitive, but no appreciable modifications of sensitivity reactions were observed either during or after administration of ascorbic acid. The authors noted, in agreement with others, that the fall in the number of platelets does not closely parallel the severity of the purpuric manifestations associated with sensitivity reactions and, therefore, concluded that a capillary defect is largely responsible for the bleeding tendency.

A case is reported by Gorrie[223] of thrombopenic purpura following seven injections of neoarsphenamine which was successfully treated with vitamin P. However, the blood picture indicated that in this case the patient was suffering from generalized myeloid hypoplasia, and the favorable result may be attributed to the self-limited course of the process.

Forty-two cases of thrombopenic purpura following ingestion of sedormid (allylisopropylacetylcarbamide) have been compiled from the literature by Falconer and Schumacher.[224] In the 36 cases in which the sex was reported, 24 of the patients were females and 12 were males. There appeared to be increased susceptibility among older persons. The authors report an additional case, with observations of the marrow. Granulocytic elements were increased, whereas erythropoiesis appeared to be reduced, although the change may have been merely relative. The number of megakaryocytes seemed to be unaffected. Administration of vitamin C was without therapeutic effect.

A case of thrombopenic purpura developing during the course of gold therapy is described by Invaldi and Gaspary.[225] Many megakaryocytes were observed in the sternal marrow of their patient, who subsequently recovered.

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222. Falconer, E. H.; Epstein, N. N., and Mills, E. S.: Purpura Haemorrhagica Due to Arsphenamine: Sensitivity in Patients as Influenced by Vitamin C Therapy, Arch. Int. Med. **66**:319 (Aug.) 1940.

223. Gorrie, D. R.: Purpura Haemorrhagica After Arsenic Therapy Treated with Vitamin P, Lancet **1**:1005, 1940.

224. Falconer, E. H., and Schumacher, I. C.: Purpura Haemorrhagica Due to Ingestion of Sedormid (Allylisopropylacetylcarbamide): Experimental Observations and Report of Case, Arch. Int. Med. **65**:122 (Jan.) 1940.

225. Invaldi, A., and Gaspary, F.: Púrpura hemorrágica en el curso de la crisoterapia, Rev. méd. de Rosario **30**:475, 1940.

Two cases of thrombopenic purpura due to sulfapyridine are reported by Russell and Page.[226] In 1 death occurred. Examination of the marrow revealed slight increase in megakaryocytes and active erythropoiesis.

A case reported by Regamey [227] is of especial interest because the provocative agent, the type of onset and the associated symptoms are more characteristic of Henoch's purpura than of thrombopenic purpura. A 28 year old woman was vaccinated, with a marked "take," and five weeks later suffered an abrupt attack of severe abdominal pain, followed by epistaxis, hematemesis, melena and metrorrhagia. Examination revealed generalized petechiae, ecchymoses and hemorrhagic pustules. The platelet count was 30,000 per cubic millimeter, and the sternal marrow contained many immature megakaryocytes. Recovery was rapid, and one month after the hemorrhagic episode the blood and marrow were entirely normal.

Alt, Carroll and Doherty [228] report the case of a young primipara in the sixth month of gestation who was admitted to the hospital because of acute catarrhal jaundice. On admission the number of platelets was approximately 175,000 per cubic millimeter, and in other respects the blood was normal, except for leukopenia. Soon thereafter the platelets disappeared completely from the blood, and severe hemorrhagic manifestations occurred. Capillary resistance was decreased. After three weeks of serious illness, the jaundice and purpura disappeared and the patient went on to uneventful delivery.

Nonthrombopenic Purpura: All patients exhibiting a hemorrhagic tendency should have the benefit of a capillary resistance test, according to Madison and Squier.[229] Impaired capillary integrity has been associated, in their experience, with vitamin C deficiency, severe infections, the terminal phase of neoplastic disease, malignant hypertension, primary blood dyscrasias, allergic states and ovarian disorders.

Children manifesting vascular purpura due to various causes were treated with a vitamin P concentrate by Kugelmass.[230] Cases of nutritional deficiency, allergy, infection and trauma were represented. The medication employed was 150 mg. of a solution of eriodictyol glucoside

226. Russell, H. K., and Page, R. C.: Thrombocytopenic Purpura Due to Sulfapyridine, Am. J. M. Sc. **200**:495, 1940.

227. Regamey, E.: Crise aigüe de purpura thrombopénique consécutive à une généralisation vaccinale tardive, Schweiz. med. Wchnschr. **70**:697, 1940.

228. Alt, H. L.; Carroll, H. B., and Doherty, C. C.: Thrombopenic Purpura Associated with Catarrhal Jaundice: Report of a Case During Pregnancy, Quart. Bull. Northwestern Univ. M. School **14**:183, 1940.

229. Madison, F. W., and Squier, T. S.: Bleeding Due to Capillary Defect, Wisconsin M. J. **39**:31, 1940.

230. Kugelmass, I. N.: Vitamin P in Vascular Purpura, J. A. M. A. **115**: 519 (Aug. 17) 1940.

and hesperidin, administered orally each day. Successful results were obtained in all cases except those of traumatic or mechanical vascular purpura.

A case of Henoch's purpura complicated by intussusception, occurring in a boy of 3 years, is reported by Schwartzman.[231] A number of similar instances are to be found in the literature before 1940.

Reid [232] reports the case of a 71 year old woman who had suffered with prolonged bleeding and recurring hematomas for many years. The platelets numbered more than 1,000,000 per cubic millimeter, and megakaryocytes were unusually numerous in the bone marrow. According to the author, 5 similar cases have been recorded in the literature. Characteristics of the disorder include prolonged bleeding time, normal coagulation time, platelets often in excess of 1,500,000 per cubic millimeter and leukocytosis, with a white cell count ranging from 12,000 to 43,000 per cubic millimeter. There are neutrophilia, occasionally monocytosis and sometimes eosinophilia. Examination of the blood revealed myelocytes in 3 cases and myeloblasts in 1. The spleen was enlarged in 4 cases, and examination of the bone marrow in 3 revealed increased erythropoiesis and granulopoiesis and excessive numbers of megakaryocytes and platelets.

Hereditary conditions characterized by a tendency to bleed are classified by Bruun [233] as hemophilia, essential thrombopenia (Werlhof) and hereditary thrombasthenia, or pseudohemophilia (Glanzmann). To this list he adds a condition observed among 23 members of a single family, including four generations. Of these, 15 exhibited a definite bleeding tendency and 3 others had some evidence of a hemorrhagic disorder. Common to all the subjects were normal coagulation and bleeding times and normal number of platelets. Although this condition may be identical with that described by Glanzmann as hereditary thrombasthenia, the author obtained no evidence of pathologic platelet behavior. He prefers the term hereditary hemorrhagic diathesis to a more specific designation.

Hemophilia: Few contributions to the literature on hemophilia appeared during 1940. Dam and Venndt [234] report experiments on heparinized plasma of hemophilic and of normal persons designed to determine the coagulating effects on such plasma of tissue extracts and platelet suspensions. The results indicated that the coagulation defect in hemophilia consisted of reduced ability of the plasma to clot in the

231. Schwartzman, J.: Henoch's Purpura with Intussusception, Arch. Pediat. **57**:389, 1940.

232. Reid, J.: Haemorrhagic Thrombocythaemia, Lancet **2**:584, 1940.

233. Bruun, E.: Hereditary Hemorrhagic Diathesis, Acta med. Scandinav. **102**:639, 1939.

234. Dam, H., and Venndt, H.: Observations on the Coagulation of Blood Plasma in Hemophilia, Lancet **1**:70, 1940.

presence of small quantities of tissue extract, such as might be liberated from mechanically damaged cells, whereas no difference in the clotting behavior of hemophilic and of normal plasma was found when large quantities of tissue extract were employed. The use of platelet suspensions revealed a greater difference in the clotting responses of the two types of plasma than was observed when tissue extracts were added.

A review of hemophilic arthropathies, together with the presentation of 5 cases, with roentgenograms, is published by Caffey and Schlesinger.[235] The authors describe the characteristic features produced by intra-articular, intraosseous and subperiosteal hemorrhages. Dysgenesis was present in the capitulum of the radius in 2 cases and in the proximal epiphysis of the femur in 1 case.

Oxalic acid was given intravenously in doses of 3 to 12 mg. daily to 3 hemophilic patients by Page, Russell and Rosenthal.[236] They report that within two or three days after this treatment was begun the coagulation time became normal. When the drug was discontinued the clotting time returned to its previous value. No evidences of toxicity of the drug were observed. The authors suggest that oxalic acid may alter the surface tension of the platelet membrane in such a way that disintegration occurs more readily. The treatment may be of value in controlling hemorrhagic episodes of hemophilic patients.

A note on the progress of 3 patients suffering with hemophilia is given by Lawson and Graybeal.[237] In a previous article concerning these patients the authors reported on treatment by venesection. Since the last report 2 of the patients have died as the result of hemorrhage.

A competent review of the recent literature on hemophilia, with a discussion of therapeutic agents used in this disease, has been published by McGavack.[238]

AGRANULOCYTOSIS

A perusal of the literature for the past year has not revealed any new information dealing with agranulocytosis which will lead to an important revision of our ideas concerning the cause, diagnosis or treatment of the disease. It is of interest, however, that the history

235. Caffey, J., and Schlesinger, E. R.: Certain Effects of Hemophilia on the Growing Skeleton: Some Roentgenographic Observations on Overgrowth and Dysgeneses of Epiphyses Associated with Chronic Hemarthrosis, J. Pediat. **16**:549, 1940.

236. Page, R. C.; Russell, H. K., and Rosenthal, R. L.: Effect of Oxalic Acid Intravenously on Blood-Coagulation Time in Three Hemophiliacs, Ann. Int. Med. **14**:78, 1940.

237. Lawson, G. B., and Graybeal, A. B.: Hemophilia Treated by Venesection, J. A. M. A. **114**:2299 (June 8) 1940.

238. McGavack, T. H.: Some Recent Advances in the Treatment of Hemophilia, M. Clin. North America **24**:791, 1940.

of 1 case is presented in which the condition was apparently due to alurate (allylisopropylbarbituric acid). This is the most convincing evidence that a barbiturate can be responsible for the syndrome. In 1 instance it was suggested that acetophenetidin was the responsible etiologic agent, but the evidence was purely circumstantial. Cases continue to be recorded in which the disease was due to aminopyrine, prescribed in such proprietary preparations as pyramidon and causalin. A number of cases in which the condition was attributed to sulfanilamide or to sulfapyridine were reported last year. It had been rather generally assumed that the condition did not arise from sulfapyridine until 50 Gm. or more had been given, but the literature for the year contains data which appear to refute this belief. An increasing number of cases have occurred in which the condition was due to gold therapy, which is understandable on account of the greater use of gold salts in the treatment of arthritis.

Drevermann and Gardner [239] state that, although in a majority of the cases agranulocytosis can be attributed with a high degree of probability to known causal agents, there still remains a small proportion in which the disease must be regarded as idiopathic. Although the condition may occur as the result of any one of many drugs, the etiologic relationship is clearly defined only in the case of aminopyrine and its derivatives. This is because it is only for the leukopenia due to this drug that the criteria of Kracke have been fulfilled, namely: 1. It is necessary for the drug to produce leukopenia in a patient who has recovered. 2. Other leukocytic depressants must be eliminated. 3. The leukopenia must be differentiated from that of sepsis or of other blood dyscrasias. An excellent review is given of knowledge regarding the symptoms and signs, the differential diagnosis, the pathologic lesions and treatment of the syndrome. The authors recommend, as the best form of therapy, pentnucleotide and yellow bone marrow given simultaneously. It is their opinion that each plays a part in the maturation of the polymorphonuclear cell. In some cases, they believe liver extract may be beneficial. Six patients with agranulocytosis were treated with yellow bone marrow and pentnucleotide, and the response was such that the authors believe the preparations to be effective. The same type of treatment was tried for patients with myelogenous leukemia, lymphatic leukemia, monocytic leukemia and aplastic anemia, but it was ineffective.

Strumia,[240] in a general article on the changes in the leukocytes in which leukopenia is discussed, states that physiologic leukopenia is

239. Drevermann, E. B., and Gardner, H. J.: Schultz Syndrome (Granulocytopenia), with Special Reference to Its Treatment with Extract of Yellow Bone Marrow, M. J. Australia **1**:851, 1940.

240. Strumia, M. M.: Clinical Interpretation of Leukocytic Pictures, Pennsylvania M. J. **43**:1556, 1940.

rare. Occasionally a person otherwise in perfect health will have a white blood cell count between 4,000 and 5,000 per cubic millimeter. Counts below 4,000 per cubic millimeter must be considered as abnormal. The most common causes of leukopenia are infection, such poisons as benzene compounds, exposure to roentgen rays or to radium, disease of the bone marrow (aplastic anemia, agranulocytosis, pernicious anemia and myelophthisic disease), anaphylactic shock and malnutrition. He emphasizes that the most severe form of leukopenia occurs in agranulocytosis.

Pewny [241] has attempted to establish a syndrome which he has termed agranulocytosis forme fruste, but the clinical and hematologic features described do not convince one that such a clinical entity exists. The condition, he claims, is characterized by epistaxis and a tendency to bleed which may prove "mortal" if a surgical operation is performed when a patient is in this state. The syndrome is said to be characterized also by leukopenia, with a reduction in the number of granular cells of the circulating blood; the polymorphonuclear cells show a definite shift to the left, even to the development of a "myeloid reaction." The author states that such patients have transient and mild damage to the bone marrow as evidenced by a delay in the maturation process of the granulocytes and the megakarocytes. Treatment recommended is symptomatic, with the administration of almost all drugs which have been employed in the treatment of true agranulocytosis.

Lin and Isaacs [242] found that a single injection of the water-soluble potassium salt of dicarboxybenzanthracene into Swiss mice is followed by a striking decrease in the number of polymorphonuclear neutrophils. The absolute number of these cells fell from an average of 5,448 to one of 1,299 per cubic millimeter during the third week after an injection. There was a slower and more moderate decrease in the number of monocytes, with but slight change in the number of lymphocytes, eosinophils and basophils. Recovery is complete seven weeks after the last injection. Further studies may lead to the development of a method whereby experimental agranulocytosis may be produced in animals.

Day and associates [243] report that when young rhesus monkeys were given a diet essentially the same as the Goldberger black tongue–producing diet, leukopenia, with a white cell count as low as 700 cells per cubic millimeter, anemia, gingivitis and diarrhea developed and

241. Pewny, W.: Agranulocytosis Forme Fruste, New York State J. Med. **40**: 1236, 1940.

242. Lin, H. A. C., and Isaacs, R.: Production of Neutropenia in Swiss Mice by Injection of Potassium Dicarboxy-Benzanthracene, Proc. Soc. Exper. Biol. & Med. **43**:551, 1940.

243. Day, P. L.; Langston, W. C.; Darby, W. J.; Wahlin, J. G., and Mims, V.: Nutritional Cytopenia in Monkeys Receiving Goldberger Diet, J. Exper. Med. **72**: 463, 1940.

the animals died. Supplementing this diet with ascorbic acid, thiamine hydrochloride, nicotinic acid and riboflavin failed to prevent the appearance of the syndrome. The addition of the combination of ascorbic acid and liver extract was effective, as was a supplement of a crude liver extract. The ash of liver extract, however, failed to maintain a normal blood picture or to prolong life. The authors concluded that the diet was deficient in a substance which they had previously termed vitamin M and that this deficiency was responsible for the pathologic changes. While these experimental results may not have a bearing on acute agranulocytosis, they may offer an explanation for some of the chronic types of granulocytopenia of which the etiologic relations are unknown.

A case of granulocytopenia following barbiturate therapy, reported by Hadler,[244] is of extreme interest and importance because convincing evidence is presented that agranulocytosis did develop following test doses of alurate. The patient, a married woman aged 30, had previously been healthy, except for several attacks of asthmatic bronchitis. She was first admitted to the hospital on account of an infection of the upper respiratory tract and bronchitis. At this time, it was observed that the administration of allonal was followed by a shaking chill and a period of malaise. Before January 1939 allonal consisted of alurate and aminopyrine, but since then each dose has been composed of 1 grain (0.06 Gm.) of alurate and 3 grains (0.19 Gm.) of acetophenetidin. It was suspected that the patient was sensitive to alurate and as a test ⅓ capsule (0.07 Gm.) of sodium alurate was given on the evenings of August 1 and 2. On August 3 the total white cell count was 2,800 per cubic millimeter and the percentage of polymorphonuclears 63. The number of polymorphonuclear leukocytes remained low; on August 8 the total white cell count was 1,800 per cubic millimeter and no polymorphonuclear cells were present. After she ingested the drug, the patient's body temperature rose to 102 F., and she had chills and sweats. The gums became sore, and two spots of exudate appeared in the right tonsillar region. The patient made a complete recovery after the use of reticulogen (a concentrated liver extract) and pentnucleotide. Although this article is based on a single case history, it is one of great importance, for it brings up again for discussion the possibility that barbiturates may be responsible for the production of agranulocytosis. A great deal has been said about this in the past, and practically all observers had reached the conclusion that this type of drug was not responsible for the syndrome. Now, this case report is presented which appears to offer convincing evidence that this particular type of barbiturate may be a causative agent. Certainly, proved cases are rare. The author

244. Hadler, A. J.: Granulocytopenia Following Barbiturate Therapy: Report of Case, New England J. Med. **222**:755, 1940.

points out that alurate (allylisopropylbarbituric acid) and sedormid (allylisopropylacetaylcarbamide) are similar in structure. The latter drug, in recent years, has been known to produce thrombopenic purpura, and occasionally its use has been followed by a rather marked leukopenia, although it has not caused true agranulocytosis.

Kopp [245] reports the case of a patient who had a chronic and symptomatic leukopenia of four and one-half years' duration, which terminated fatally in typical agranulocytic angina. On each examination of the blood during 1934 and 1938 the patient presented a decided reduction in the number of leukocytes, with counts as low as 1,000 per cubic millimeter. The various white cell elements were quantitatively but not qualitatively affected. No cause could be found for the leukopenia, and although the reduction of white cells was at times striking, the patient enjoyed good health for four and one-half years. No examinations of the blood were made between 1934 and 1938; so it is not known whether the leukopenia was present in the interim. Until the onset of the acute disease the patient had taken only potassium iodide, acetylsalicylic acid and sodium amytal. Just prior to the development of the fatal agranulocytosis he was given fairly large doses of preparations containing acetophenetidin. On the patient's admission to the hospital, the white cell count was found to be 350 per cubic millimeter and only a few granular cells were noted on the blood film. Treatment was with a transfusion and adenosine sulfate. Kopp believes that this case strongly supports the theory that agranulocytic angina tends to occur in persons in whom a bone marrow dyscrasia is already present, with a resultant diminution of the granular cells in the peripheral blood stream.

The case of a white woman aged 41 in whom agranulocytosis developed after the use of capsules containing aminopyrine and codeine sulfate for the relief of uterine symptoms is reported by Bailey and Katzen.[246] Later ulcerative lesions of the mouth developed, for which therapy with azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene 3′,6′-disulfonate) was instituted. It appeared to the authors that this substance "caused further destruction of the granulocytes." Twelve hours before death examination of the blood yielded the following information: red cell count 3,400,000 per cubic millimeter, percentage of hemoglobin 70 and white cell count 200 per cubic millimeter. Examination of a blood film showed complete absence of neutrophils. The patient died twelve hours after

245. Kopp, I.: Chronic Leukopenia with Fatal Termination Due to Agranulocytic Angina: Case Report, Ann. Int. Med. **13**:2347, 1940.

246. Bailey, J. H., and Katzen, B.: Case of Agranulocytosis Following Use of Pyramidon and Neoprontosil, Virginia M. Monthly **67**:112, 1940.

treatment was instituted with an oxygen tent, administration of pentnucleotide and blood transfusion.

Berghausen [247] states that when aminopyrine is prescribed the physician should be on the alert for possible toxic symptoms. Unfortunately, it is not always recognized that a drug bearing a trade name contains aminopyrine. Such a drug is causalin, each 7.5 grain (0.5 Gm.) tablet of which was stated by Berghausen, citing Bernhard, to contain 1.82 grains (0.12 Gm.) of aminopyrine. He reports the case of a 52 year old woman who had been taking such a tablet three times daily for a month, on the advice of her physician, for the relief of arthritis. An acute illness developed. On admission to the hospital the patient was exceedingly toxic, the temperature was 102 F., there was ulceration on the hard palate and the pharynx was swollen and edematous. The white blood cells numbered 1,150 per cubic millimeter, and there were no granular cells present in the stained blood film. Sternal puncture showed that all of the white cells were lymphocytes, the red blood cells were normal in size and normoblasts were absent. The patient died on the day following admission. The only therapy was a 10 per cent solution of dextrose given intravenously.

It is pointed out by Mirick [248] that since the introduction of sodium gold thiosulfate by Mollgaard, of Copenhagen, Denmark, in 1924, the popularity of gold salts as therapeutic agents has steadily increased in treatment of tuberculosis, chronic rheumatism, lupus erythematosis and various other diseases. The reluctance to utilize gold salts in this country has been due to the fear of toxic reactions, which have been carefully reported and analyzed by Hartfall, Garland and Goldie.[249] Mirick has reviewed the cases reported in the literature, collected 17 other cases and added one of his own, in which there was complete agranulocytosis with recovery. The patient was a woman aged 22 who had suffered from rheumatoid arthritis and questionable pulmonary tuberculosis for one year. She received a total dose of 0.825 Gm. of sodium gold thiosulfate, chiefly intramuscularly, over an interval of twenty-one days. The first indication of a hematologic complication appeared at the end of that time, when it was noted that the total leukocyte count was 3,880 per cubic millimeter and the percentage of polymorphonuclear cells and basophils was 22. The diminution in the number of granulocytes became progressively greater, until twelve days later they completely disappeared from the blood stream. There was

247. Berghausen, O.: Fatal Leukopenia Following Internal Administration of Causalin, J. A. M. A. **114**:1547 (April 20) 1940.

248. Mirick, G. S.: Total Agranulocytosis Following Gold Therapy: Report of Case with Recovery and Review of Literature, Am. Rev. Tuberc. **41**:344, 1940.

249. Hartfall, A. J.; Garland, H. G., and Goldie, W.: Gold Treatment of Arthritis: Review of Nine Hundred Cases, Lancet **2**:784 and 838, 1937.

no significant change in the red blood cells at any time. The only other untoward symptom associated with gold therapy was a mild and transient cutaneous rash, which appeared a few days after the granulocytopenia became apparent. After complete agranulocytosis had been present for three days, the polymorphonuclear cells reappeared, and their percentage and the total leukocyte count returned to normal. This recovery followed the administration of liver extract, blood transfusions, pentnucleotide and ferrous sulfate. The only other drug used was sodium amytal, which was employed for sedation. There was no history of the ingestion of other drugs which might have been responsible for the agranulocytosis. Despite the unpleasant and serious complication following the gold therapy, the patient experienced striking improvement in her rheumatic complaints and left the hospital feeling better than she had at any time since the onset of her illness.

An excellent and comprehensive summary of the previously reported cases in which agranulocytosis developed after gold therapy is given by Mirick. In 18 such case reports studied, there were 9 instances of "rheumatism" and 9 of tuberculosis, 14 patients were female and 4 were male and 9 patients died and 9 recovered. The interval between the first injection of gold salts and the onset of the agranulocytosis varied from twelve to about one hundred and eighty days; in 9 cases the interval was thirty days or less. Five different gold preparations were given, as follows: crisalbine (sodium gold thiosulfate), sanocrysin (sodium gold thiosulfate), allochrysin (sodium aurothiopropanol sulfonate), solganol B (aurothiodextrose) and lopion (sodium auroallylthiourea benzoate).

There is no evidence that incriminates any one preparation, nor does the dosage appear to play a role in either the causation of the complication or the prognosis. The latter conclusion is supported by the fact that the patients who died received between 0.8 and 3.5 Gm. of the salt, with an average of 1.29 Gm., whereas the patients who recovered received from 0.08 to 4.5 Gm., with an average of 1.26 Gm. On the other hand, the author claims that there is some prognostic information of value to be derived from the absolute number of polymorphonuclear cells and basophils present in the circulating blood. He notes that in those cases in which the absolute number was below 34 the mortality was 75 per cent, whereas if the lowest number was 36 or more, recovery followed in all cases. He also states that the presence of eosinophilia is a good prognostic sign. It is concluded that the evidence incriminating gold salts as a cause of agranulocytosis is circumstantial and therefore presumptive. Agranulocytosis has occurred in the past, not infrequently, in patients with "chronic rheumatism" because they have been prone to employ aminopyrine therapeutically. This cannot be said, how-

ever, to apply necessarily to patients with tuberculosis. The only conclusive evidence that the disease can be due to gold salts must be obtained by producing the condition experimentally in animals or in patients who have previously experienced an attack. A warning is given not to administer gold salts to patients who have hepatic disease, hemorrhagic states, allergic conditions or eczema. There is no evidence that cutaneous tests with gold preparations will enable one to avert untoward complications. The author concludes that agranulocytosis supervenes in about 1 case in 1,000 in which gold salts are given; in about one half of the cases in which this condition develops the patients recover, and in an equal number they succumb; neither age, sex, underlying disease, dosage of the gold salts, the preparation employed nor length of time between the onset of therapy and appearance of the agranulocytosis seemed to make any difference in the prognosis. In his opinion, the relationship between the gold salts and the blood changes remains unsettled, but the cases reported support the concept that gold may be the cause of agranulocytosis in some cases. The article is one of singular value on account of the adequately detailed case report and the admirable review of the literature.

Anderson and Palmer [250] state that gold salts are being used with increasing frequency in the treatment of arthritis, lupus erythematosis, cutaneous tuberculides and syphilis. Among the hematologic complications which may develop after such therapy are purpura, granulocytopenia, hypochromic anemia and aplastic anemia. This article is a complete summary of all the untoward complications which may follow the administration of gold preparations.

Sweeney and Allday [251] reemphasize that physicians who give sulfanilamide to patients should be on the alert for the development of agranulocytosis, which will appear in the occasional person who is susceptible to the drug. They report the case of a woman aged 41 who received 20 Gm. of sulfanilamide over a period of eight days for acute pharyngitis. At the end of this time the white cell count was 1,800 per cubic millimeter, with 4 per cent polymorphonuclear cells, the red cell count was 2,680,000 per cubic millimeter and the hemoglobin concentration was 42 per cent. Treatment consisted of daily transfusions of 300 cc. of blood for seven days. At this time there was a "remarkable" crisis, characterized by a critical drop in the body temperature to subnormal, a striking increase in the polymorphonuclear cells and evidence of general improvement in the patient. The crisis described resembles

250. Anderson, N. L., and Palmer, W. L.: The Danger of Gold Salt Therapy: Report of Fatal Case, J. A. M. A. **115**:1627 (Nov. 9) 1940.

251. Sweeney, J. S., and Allday, L. E.: Granulocytopenia from Sulfanilamide with Unusual Blood Crisis and Recovery: Case Report, Ann. Int. Med. **13**:1241, 1940.

that seen in pneumonia. We also have observed similar and dramatic improvement in patients with agranulocytosis, although previous mention of this has not been observed in the literature.

A case of agranulocytosis is reported by Robb [252] in which ingestion of 36 Gm. of sulfanilamide over a period of three weeks was followed by death. This medicament was obtained by the patient from a drugstore, apparently without a prescription, for the treatment of a urethral discharge. He was admitted to the hospital with a high fever and the following day complained of sore throat. On admission he had 2,400 white blood cells per cubic millimeter, with no granulocytes present in the blood film; the hemoglobin concentration was 59 per cent, and the red blood cell count, 3,520,000 per cubic millimeter. He died on the fifth day in the hospital, despite the use of 120 cc. of pentnucleotide for four days, the injection of liver extract daily and three blood transfusions. The clinical diagnosis was acute agranulocytosis due to sulfanilamide, with terminal bronchopneumonia. At necropsy, the striking feature of the bone marrow was the presence of few granular cells.

Anderson, Horowitz and Palmer [253] report the case of a 32 year old woman with a mild "simple" anemia, an inflamed throat and an infection of the urinary tract, in whom pleuropneumonia developed. Treatment was with sulfapyridine, and she received 75 Gm. in divided doses over a month. The blood at the end of this time showed 38 per cent hemoglobin and 1,210,000 red cells and 1,940 white cell per cubic millimeter. The following day the white cell count was 3,800 per cubic millimeter, with 24 per cent granulocytes. Sternal puncture showed an enormous increase in myelocytes and myeloblasts in the marrow and almost complete absence of older forms of these cells. Treatment was with pent nucleotide in an 8 per cent solution, 10 cc. being given intramuscularly in four doses in the three days preceding death. Also, liver extract was administered, without avail. The patient was considered to have a "maturation type" of agranulocytosis occurring after the use of sulfapyridine. The results of necropsy were consistent with this diagnosis.

Tragerman and Goto [101] warn against the use of sulfanilamide and its derivatives without adequate supervision, as fatal complications due to granulocytopenia, hemolytic anemia and damaged liver may occur. Three of the 5 deaths following sulfanilamide or sulfapyridine therapy encountered in the autopsy service of the Los Angeles County Hospital

252. Robb, J. P.: Fatal Case of Agranulocytosis Following Use of Sulfanilamide, Canad. M. A. J. **42**:268, 1940.

253. Anderson, W. K.; Horowitz, S., and Palmer, T. W.: Fatal Agranulocytosis After Sulfapyridine (M. & B. 693) Therapy, Glasgow M. J. **134**:172, 1940.

were due to granulocytopenia. One patient was a boy aged 15 who received 100.6 Gm. of sulfanilamide over a period of eighteen days. Three days after the drug had been discontinued, sore throat developed, with a body temperature of 104 F., reddened pharynx and injected ear drums. The white blood cell count was 675 per cubic millimeter, with no polymorphonuclear cells. The boy died on his second day in the hospital. Necropsy showed a reduction in the granulocyte series of cells, with arrest of maturation at the myelocyte level. A second patient was a 35 year old woman who took 64 Gm. of sulfanilamide over a period of two weeks for a "streptococcic sore throat." Despite treatments with blood transfusions, pentnucleotide and liver extract she died on the third day of hospitalization. The bone marrow was not examined at necropsy. The third patient was a man aged 53 who had subacute bacterial endocarditis due to Streptococcus viridans, for which he was given 88.5 Gm. of sulfapyridine over a twenty-one day period. At the end of this time the patient complained of sore throat, and examination of the blood showed 1,100 leukocytes per cubic millimeter, of which 22 per cent were polymorphonuclear cells. One blood transfusion was given, but the patient died six days after the sulfapyridine therapy was discontinued. At necropsy the bone marrow showed arrest of maturation at the myeloid level.

Sakula [254] reports the case of a 2½ year old girl who recovered from meningitis caused by the Pfeiffer bacillus after the administration of sulfapyridine but in whom a granulocytopenia apparently due to the medication developed. The drug was given intermittently because of exacerbations and remissions of the disease and also because of the untoward reactions it produced. A total dose of 31 Gm. was given over a period of twenty-four days. The first evidence of agranulocytosis appeared in the form of a leukocyte count of 3,000 per cubic millimeter, with 13 per cent polymorphonuclear cells. After the omission of the drug and the administration of pentnucleotide the child made an uneventful recovery. The author states that "numerous" cases of granulocytopenia, and even of agranulocytosis, have followed the use of the drug. He considers that danger of development of such a condition must be increased in children, for, in his opinion, their bone marrow is more susceptible to toxic damage. Frequent blood counts are recommended when the drug is given in large doses and for prolonged periods.

It has been commonly considered that development of agranulocytosis following sulfapyridine therapy is usually related to the amount of the drug given and to the duration of the treatment. The average dose followed by the development of agranulocytosis has been 50 Gm. for

254. Sakula, J.: Pfeiffer Bacillus Meningitis Successfully Treated with M. and B. 693, Complicated by Granulopenia, Lancet **1**:596, 1940.

an average period of twenty days. Spain [255] reports a case in which, he claims, the condition appeared after the administration of 4.5 Gm. of sulfapyridine and 4.5 Gm. of sulfanilamide over an interval of four days. The patient was a primipara aged 26 who was given the drugs on account of acute mastitis which developed ten days after a cesarean section. Three days after the medication was discontinued, the patient complained of a "sore throat" and the white blood cell count was found to be 1,920 per cubic millimeter, with 2 per cent granular cells. Despite treatment with pentnucleotide and blood transfusions, the patient died on the fifth day of her illness. Ordinarily, the presence of anemia casts doubt on the diagnosis of true agranulocytosis, as the leukopenia under such circumstances is often associated with some other type of blood dyscrasia, such as aplastic anemia or aleukemic leukemia. In this patient the hemoglobin concentration was 36 per cent and the red cell count 2,490,000 per cubic millimeter, which values could be accounted for by the drugs employed or by the presence of an iron-deficiency anemia of pregnancy and the loss of blood at the operation, which was reported as "moderately heavy." In other words, there is no reason why agranulocytosis might not develop in a patient with anemia.

Montuschi [256] reports a case of agranulocytosis in a 15 month old infant after 17.5 Gm. of sulfapyridine had been administered over a period of eight days. Twenty-four hours after the treatment had been initiated the sulfapyridine content of the spinal fluid was 8 mg. per hundred cubic centimeters, and in fifty-two hours it was 4 mg. per hundred cubic centimeters. After the temperature had decreased and other striking evidences of improvement appeared, the temperature again rose. This change led to an examination of the blood, and it was found that the total white cell count was 6,000 per cubic millimeter but that only 21 per cent of the cells were granulocytes. No ulcerative lesions of the mouth appeared at any time. The lowest absolute number of granulocytes during the course of the illness was 400 per cubic millimeter. Eosinophils reappeared in the blood on the fifth day of treatment with pentnucleotide, and this was promptly followed by the subsidence of all symptoms and complete recovery. The author is not entirely willing to credit the pentnucleotide with the cure, as he states that recovery may have been spontaneous. In such cases, however, he apparently considers its use advisable.

Leftwich [257] reports the case of a native laborer who was admitted to the hospital with lobar pneumonia, for which he was given 42 Gm.

255. Spain, A. W.: Agranulocytosis Following Chemotherapy with Small Dosage, Brit. M. J. **1**:930, 1940.

256. Montuschi, E.: Granulocytopenia Following Sulphapyridine Therapy, Brit. M. J. **1**:1055, 1940.

257. Leftwich, P.: Agranulocytosis Complicating Treatment by Sulphapyridine (M. and B. 693), South African M. J. **14**:142, 1940.

of sulfapyridine over a period of twenty-one days. At the end of this time, because of the recurrence of fever, his blood was again examined and the total white cell count found to be 1,400 per cubic millimeter. No granulocytes were present, nor were any observed in the next three days before death. The author states that in most cases this syndrome develops after a total dose of 45 Gm. has been given, although he refers to 1 case in which only 18 Gm. of the drug had been taken in fifteen days. He warns that a rare case of agranulocytosis must be expected to appear, especially when the total dose is over 50 Gm. In any patient receiving the drug, the development of leukopenia should be suggested by a sudden aggravation of the toxemia, high fever, generalized aching or sore throat.

Erskine and Royds [258] report the case of a man aged 29 in whom acute pemphigus developed nine days after he received a burn. As treatment a total of 35 Gm. of sulfapyridine was administered over a period of twenty-one days. At the end of this time the leukocyte count was 6,000 per cubic millimeter, with only 17 per cent of the cells of the polymorphonuclear type, 90 per cent of which were immature. There was also a fairly severe associated anemia, as the hemoglobin concentration was 52 per cent and the red cell count 2,860,000 per cubic millimeter. The case is reported as one of agranulocytosis due to the ingestion of 35 Gm. of sulfapyridine, with recovery following the discontinuance of the drug and the administration of liver extract and pentnucleotide.

Forkner, in "Conferences on Therapy," [259] expresses the belief that agranulocytosis is an acute episode with a definite syndrome which goes on either to death, in about 70 per cent of the cases, or to spontaneous, or possibly induced, recovery, in the remaining 30 per cent. His attitude is one of pessimism in regard to the effectiveness of any therapeutic agent which has been employed in this disease. This is indicated in the following statement:

> As a matter of fact there has been no satisfactory study of a treated group of cases of agranulocytic angina and a control group comparable as to age, nutrition, general state of health and blood picture in which any therapeutic agent has been shown to be beneficial.

The most important factor in the treatment, he believes, is to remove the offending agent, if it can be found. Roentgen ray therapy he considers to be dangerous; there is no good evidence to support the view

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258. Erskine, D., and Royds, J. E.: Agranulocytosis Complicating Treatment of Acute Pemphigus with M. & B. 693, Lancet **2**:1366, 1939.

259. Conferences on Therapy (From Cornell University Medical College and New York Hospital): Treatment of Blood Disorders; Leukemia, Agranulocytosis and Neutropenia, J. A. M. A. **115**:126 (July 13) 1940.

that liver extract is helpful; pentnucleotide is not as effective as it was once thought to be, and observations do not indicate that blood transfusions are of value. We do not agree with Forkner in labeling as useless all forms of treatment which have been suggested for agranulocytosis. It is his opinion that evidence does exist which suggests strongly that pentnucleotide and blood transfusions are superior to other forms of therapy and should be employed in all cases.

INFECTIOUS MONONUCLEOSIS

During the past year probably the most important contribution to the literature dealing with infectious mononucleosis is the monograph by Bernstein. Other articles indicate and emphasize the importance of the diversity of the symptoms, the great diagnostic value of the heterophile antibody reaction and the presence of jaundice and anemia in some cases. The occurrence of the meningeal type of the disease, with a fatal termination in some instances, is discussed. Sulfanilamide and convalescent serum are the newest therapeutic agents which have been used. Bernstein's article [260] of 64 pages, with 207 references, will be of inestimable assistance to all physicians who are interested in the condition. A digest of its contents is not possible in a review of this nature. It is highly recommended, however, to all those who desire to obtain an idea of the development and the present status of knowledge concerning the disease.

Kracke [261] considers that infectious mononucleosis is important because many new facts concerning the disease have been learned in recent years and because its manifestations are so protean. He states that the modern interest in the condition arose in 1920, when Sprunt and Evans applied the term "infectious mononucleosis." In 1932 Paul and Bunnell again stimulated interest by the introduction of the heterophile antibody reaction, which has proved to be a reliable diagnostic test. He agrees that the disease is prone to occur in the young but states that he has observed it in a husband and wife aged 62 and 58, respectively. The oldest patient seen by any of us was a man aged 44. Kracke considers the disease to be rare, or possibly even nonexistent, in Negroes, as he has never seen a patient with such a condition in the large Negro population of the Grady Hospital in Atlanta, Ga. There is evidence that it has a worldwide prevalence. Apparently there is no seasonal incidence. Although clinically the disease appears to be infectious, there are no confirmed studies which have demonstrated the

260. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85, 1940.

261. Kracke, R. R.: Infectious Mononucleosis, Texas State J. Med. **36**:348, 1940.

causative organism. It has been claimed that monkeys can be inoculated successfully with material from infected lymph nodes. In 1 research worker the disease developed after he pricked his finger with an infected knife blade. Nyfeldt isolated an organism which he called "bacillus monocytogenes hominis" and claimed that this agent will produce the condition in dogs. Later Schmidt and Nyfeldt reported that they obtained the same organism from the spinal fluid in 4 out of 5 patients. At present it must be considered that the etiologic agent is unknown. It may possibly be a virus. Washings from the nasal cavities and throats of patients with the active disease failed to transmit it when sprayed into the throats of healthy persons. The usual clinical manifestations are described in this article, and the occurrence of the meningeal type, with an increase in lymphocytic cells of the spinal fluid, is mentioned. The prominence of abdominal pain as the leading symptom in some cases is emphasized; this symptom is attributed to swelling of the lymph glands in the mesenteric region, which has been observed at operation. Infectious mononucleosis is almost always a febrile disorder, with an increase in temperature which persists usually for one to two weeks and has an average duration of eight to twelve days. Of greatest importance in the diagnosis is the presence of enlarged and tender lymph glands preceding or following the onset of the fever. It is believed by the author that the greatest increase in lymph glands is associated with the highest leukocyte count. The spleen is moderately enlarged in 50 per cent of the cases. In 1 instance splenic enlargement which extended to the umbilicus was noted. In rare instances jaundice, which Kracke attributes to "intrahepatic obstruction," may be present. The typical finding in the blood is an increase in the white cells to from 10,000 to 20,000 per cubic millimeter, with a relative and absolute lymphocytosis. The most important diagnostic evidence of the disease is the unusual type of circulating lymphocyte. The characteristic cell is described as a large, atypical, irregularly lobulated lymphocyte having sky blue cytoplasm with a clear perinuclear zone. One of the outstanding features of this cell is the presence of small, variable-sized vacuoles which "almost stamps it without question as being a cell of infectious mononucleosis." The percentage of these unusual cells may be as high as 90, and in nearly all cases it exceeds 50. Kracke agrees that they are lymphoid in type and that their origin is probably from the involved lymphoid tissue and the spleen. It is emphasized that the red cell count and the hemoglobin content are usually normal, a valuable differential point between this disease and leukemia.

The heterophile antibody test is considered to be one of great reliability, as it established with certainty, in nearly all instances, the presence or absence of the disease. He considers a titer of 1:32 as diagnostic and states that the reaction is almost always positive early

in the course of the disease. Although we consider that this test is an exceedingly valuable one, not this much reliance is placed on it, as in our experience the reaction is often negative early in the course of the disease. It is stated that the condition may be confused with leukemia, agranulocytosis and thrombopenic purpura. Because of the enlarged glands, and particularly the positive Wassermann and Kahn reactions in some cases, it must be differentiated from syphilis. Also, various syndromes characterized by enlarged glands, such as Hodgkin's disease, tuberculosis and lymphosarcoma, should be considered. In some cases there may be a rash, easily confused with the ordinary exanthems. The author states that there is no specific treatment for the condition and that it usually runs its course in about two weeks.

Grove [262] emphasizes that infectious mononucleosis is so frequently associated with symptoms and signs involving the upper respiratory tract that it should be kept constantly in mind by the laryngologist. About three fourths of the patients have some evidence of infection of the throat, the most frequent being injection of the pharynx, hypertrophy of the lymphoid tissue and, occasionally, membrane formation. When the disease is not ushered in with the symptoms of sore throat, the initial evidences are those of influenza or of cold in the head, with a febrile reaction. An almost constant clinical finding is enlarged glands, which are most frequently present in the anterior triangle of the neck. These may persist for a long time after the patient has recovered from other symptoms. They are never known to suppurate. It is emphasized that the diagnosis can usually be made with certainty at some time during the course of the disease when the symptoms are considered along with the changes in the blood and the development of the positive heterophile antibody reaction. The laryngologist should differentiate lesions of this condition from other membranous and ulcerative lesions affecting the pharynx, such as those of diphtheria, Vincent's angina, streptococcic sore throat, agranulocytosis, syphilis and tuberculosis. The author sounds a warning against the indiscriminate use of sulfanilamide in treating this condition, as the drug may have a tendency to depress further the number of granulocytes in the circulating blood. Cases are cited to emphasize that relapses may occur after apparent complete recovery, that convalescence is slow and protracted in some cases and that the atypical lymphocytes may be present in the blood stream for many weeks after the total white cell count has returned to normal. Furthermore, the glandular enlargement may not subside for many months, and the heterophile antibody reaction may continue to be positive for fifty to two hundred and ninety days after the subsidence of the clinical signs.

262. Grove, W. E.: Laryngologic Aspects of Sporadic Infectious Mononucleosis, Arch. Otolaryng. **32**:472 (Sept.) 1940.

Hollander [263] has based his method of performing the heterophile antibody test on the principle that centrifugation offers a rapid and reliable technic for all agglutination tests. He centrifuges the mixture of sheep cells and human serum for five minutes at 1,000 revolutions per minute and, after shaking, reads for agglutination. It is claimed that in the high dilutions there is a greater sensitivity of the reaction with this method. Its greatest superiority, however, is due to the rapidity with which it can be performed. Such a rapid method will certainly be welcomed by the clinician.

According to Fowler and Tidrick,[264] there is a renewed interest in infectious mononucleosis on account of the increasing use of the Paul-Bunnell heterophile antibody test. The diagnosis is made more frequently because of this aid and because attention is focused on the disease. It is becoming increasingly apparent that there are many cases in which atypical clinical pictures are presented and that there are many pitfalls in making the diagnosis. The characteristic clinical picture is described, with which account we are in accord, except for the statement which implies that the spleen is palpable in all patients. In our experience it has been palpable in about 50 per cent or less. Emphasis is placed on the prolonged period of convalescence and on the important fact that for months, although symptomatic recovery may be complete, lymphadenopathy and splenomegaly may persist and abnormal lymphocytes may remain in the blood stream. It is emphasized that the blood picture is typical and that the characteristic change is the presence of atypical lymphocytes. A common error has been to confuse these lymphocytes with the "blast" cells of acute leukemia. Attention is directed to the occurrence of the false positive Wassermann reaction in cases of infectious mononucleosis and confusion of the condition with early syphilis. Jaundice in association with infectious mononucleosis has been previously noted, and it is emphasized that the heterophile antibody test is of great value in the differential diagnosis. It is not improbable that many cases of so-called catarrhal jaundice have actually been ones of infectious mononucleosis. The highest agglutination titer for heterophile antibodies encountered by the authors has been 1:3,584, which was reduced to 1:112 by absorption with fresh guinea pig kidney. In this case, on account of the unusually high absorption with guinea pig kidney in the test, a lymph node was removed, and this showed hyperplasia compatible with infectious mononucleosis. It is properly emphasized that the heterophile antibody test with its recent modifi-

263. Hollander, A.: Centrifuge Technique in Heterophile Agglutination Test, J. Lab. & Clin. Med. **25**:542, 1940.

264. Fowler, W. M., and Tidrick, R. T.: Unusual Manifestations of Infectious Mononucleosis, Am. J. Clin. Path. **10**:548, 1940.

cations is of such accuracy that atypical cases can be recognized. If attention is directed toward the disease so that more complete hematologic and serologic tests are done on patients with enlarged lymph glands, obscure fever and symptoms of an infection of the upper respiratory tract, a greater recognized incidence of the condition will undoubtedly result.

Lassen and Thomsen [265] state that the various clinical pictures which infectious mononucleosis presents are linked together by the characteristic blood changes and the heterophile antibody reaction, thereby forming a well defined nosographic unit, although the etiologic agent is unknown. Until recent years the treatment has been entirely symptomatic, as the disease has been considered benign, with a duration which does not exceed three weeks. More recently, however, it has been appreciated that the condition may be accompanied by a severe and sometimes necrotic angina and that symptoms may persist for several months. Moreover, it has been recognized recently that there is a meningeal type, characterized by headache, rigid neck, mental symptoms, transient paralysis, paresthesias and increased cell content of the spinal fluid. The work of Thomsen and Vimtrup is cited, in which 6 cases of fatal infectious mononucleosis were reported. It was shown that the process may localize, apparently selectively, in the respiratory center and there produce paralysis, with a fatal termination. The same authors also showed in studying over 500 cases from Blegdam Hospital, Copenhagen, Denmark, that the mortality rate is between 1 and 2 per cent. Lassen and Thomsen cite Anderson's report of 2 cases of fatal termination in Denmark. According to the authors, it is "rather probable" that more severe forms of the disease have been regarded in the past as septic angina, malignant diphtheria, meningitis or encephalitis. It is their opinion that the serologic test will afford the means of proving that the disease occasionally has a more unfavorable prognosis. In 12 cases of the most severe form treatment was with 30 to 300 cc. of convalescent serum. The results were compared with the outcome in 15 cases of severe disease in which no treatment was given, 50 cases in which nonspecific serum was used and 27 cases in which intravenous injections of neoarsphenamine were given. In those cases in which treatment was with convalescent serum there was a rapid improvement in the general condition of the patients. The body temperature fell to normal within twenty-four to forty-eight hours, and the patients had a "pronounced feeling of detoxication." In other cases sulfanilamide therapy was used, but results of this treatment will be the subject of another report. The only other reference, and this was favorable, to

265. Lassen, H. C. A., and Thomsen, S.: Treatment of Infectious Mononucleosis with Specific Convalescent Serum, Acta med. Scandinav. **104**:498, 1940.

the use of convalescent serum in the treatment of the disease is the report of Whitby and Britton, in 1939.[266]

According to Gall and Stout,[267] a survey of the literature reveals that there is no consistent lesion reported to be found in the lymph glands of patients with infectious mononucleosis. The authors removed nodes from 10 patients with the disease. They describe changes which occur with such regularity, and with such infrequency in other conditions, that they believe them to be of diagnostic significance. The picture they describe is characterized not by a single pathologic feature but by a general pattern and change in the node. The gross architectural relationships are retained; the basic process underlying the lesion is essentially the result of proliferative stimulation of the components of the nodes; the "infectious mononucleosis cells," similar to those observed in the circulating blood, are seen in the lymph nodes in small numbers; such cells are large, two or three times the size of a small lymphocyte, and have abundant basophilic cytoplasm, either granular or rather coarsely vacuolated. For the finer details of the pathologic changes and a review of the literature, reference should be made to the original article.

Robinson [268] describes the case of a man aged 29 in whom developed vague symptoms which were eventually recognized as evidence of infectious mononucleosis. This case was regarded as sporadic until further investigations indicated that there had probably been at least 3 other cases which had been overlooked. This is a situation which undoubtedly occurs frequently. A case should not be called sporadic until a careful investigation has eliminated the possibility that other cases have not been recognized.

Chapman and Chapman [269] report 7 cases of infectious mononucleosis in children and young adults, in all of whom jaundice developed a few days after the onset of symptoms. In all, the peripheral blood showed cells typical of those occurring in infectious mononucleosis. This finding, when considered with the generalized enlargement of lymph glands and such evidence of infection as fever, led the observers to conclude that they were dealing with infectious mononucleosis. The heterophile antibody reaction was not determined in any of the cases, as the facilities were not available. It was concluded that the jaundice was of the

266. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 3, Philadelphia, The Blakiston Company, 1939.

267. Gall, E. A., and Stout, H. A.: Histologic Lesion in Lymph Nodes in Infectious Mononucleosis, Am. J. Path. **16**:433, 1940.

268. Robinson, J. B.: Infectious Mononucleosis: Report of Case, Chinese M. J. **57**:473, 1940.

269. Chapman, A. A., and Chapman, J.: Infectious Mononucleosis with Jaundice, Southwestern Med. **24**:200, 1940.

obstructive type but that it was incomplete, as the stools were not clay colored. The obstruction might have been partially due to pressure from an enlarged lymph node in the region of the common duct. It is stated, however, that it is equally permissible to consider the jaundice as being due to toxic hepatitis, an explanation which we favor.

Haines and Corn [270] present the case of a girl aged 13 in whom the usual symptoms of infectious mononucleosis developed. On the following day her brother became ill with all of the evidences of scarlet fever. Both were given convalescent scarlet fever serum. Within two days the boy's temperature became normal, but the girl's rose to 104 F. At this time there was redness of the pharynx but no membrane or edema of the throat. There was a suggestion of strawberry tongue. The cervical lymph nodes were enlarged, discrete and tender. There was a diffuse erythematous flush. Five grams of sulfanilamide was given over a period of three days, without material effect on the course of the disease, as the patient continued to have a septic fever for eight days despite the medication. Examination of the blood eighteen days after the onset showed a white cell count of 14,900 per cubic millimeter. The differential count revealed that 88 per cent of the leukocytes were large lymphocytes typical of infectious mononucleosis. The red cells showed rather remarkable evidence of regeneration, as indicated by polychromatophilia, basophilic stippling and the presence of an occasional normoblast. The hemoglobin percentage and the erythrocyte count were not stated. Also, occasional promyelocytes and myelocytes were seen, as well as a rare cell which was interpreted to be a "leukoblast." The heterophile antibody reaction was reported positive in a dilution of 1:150. The patient made a complete recovery and remained well until eighteen days later, when acute suppurative appendicitis developed, a diagnosis confirmed by operation. At this time her leukocyte count was 18,300 per cubic millimeter, with a differential count of 45 per cent lymphocytes, 7 per cent monocytes and 48 per cent polymorphonuclears. The case was reported because the blood picture varied from that usually observed in infectious mononucleosis, as there were anemia, evidence of red blood cell regeneration and a mild leukemoid reaction. It was suggested that these changes were due to the administration of sulfanilamide.

Priestley [218] reports the case of a woman aged 25 who had the syndrome of thrombopenic purpura for which a splenectomy was performed uneventfully. Two weeks after the operation fever developed, with a number of swollen tender glands in the neck, axillas and groins. The fever, which was of the remittent type, was present for several

270. Haines, D. J., and Corn, H. H.: Infectious Mononucleosis with Mild Leukemoid Reaction: Report of Case, J. Iowa M. Soc. **30**:430, 1940.

weeks. About one week after the onset of the fever, the white blood cell count was 10,200 per cubic millimeter, with 52 per cent neutrophils, 25 per cent lymphocytes, 3.5 per cent monocytes, 2 per cent eosinophils, 2 per cent basophils and 15.5 per cent unclassifiable mononuclear cells. The Paul-Bunnell reaction was negative. About ten days later the white blood cell count was 15,950 per cubic millimeter, and of these 74 per cent were lymphocytes. The author states that the mononucleosis was difficult to explain and the diagnosis of infectious mononucleosis was made only by the successive elimination of the various forms of pyrexia associated with enlargement of the cervical lymph nodes. With the available evidence it was thought that this diagnosis was most probable, despite the negative Paul-Bunnell reaction.

Kent [271] reports the case of a boy aged 14 who had acute leukemia, probably of the monocytic type, in which the heterophile antibody reaction was positive in a titer of 1 : 4,096 when the original technic of Paul and Bunnell, described in 1932, was employed. There does not seem to be any doubt concerning the diagnosis of acute leukemia, but, as is often the case, a difference of opinion arose as to whether it was monocytic or myelogenous. The hemoglobin concentration was 42 per cent, the red blood cell count 2,110,000 per cubic millimeter and the white blood cell count 20,900 per cubic millimeter, with 82 per cent immature unclassified cells (many resembled monocytes and others myelocytes). The patient had received neoarsphenamine intravenously and sulfanilamide orally. No horse serum had been given. It is important that such a case as this be reported because the heterophile antibody reaction is recognized as one of the most reliable means of differentiating the various types of leukemia from infectious mononucleosis. Certainly it is rarely positive in cases of the leukemias. There is no statement in the case history concerning the parenteral use of liver extract, which may well have been given in a case of this type. According to Bernstein, [260] this treatment may result in the reaction becoming positive.

HODGKIN'S DISEASE

A comprehensive review of the symptomatology of Hodgkin's disease has been made by Goldman,[272] who analyzed 212 cases. The disease occurred at any age but was most prevalent during the third decade. The ratio of males to females was about 2 : 1. Hodgkin's disease was noted in every race, and no predisposing factors were observed. The most common symptoms were lymphadenopathy, loss of weight and

271. Kent, C. F.: "False" Positive Paul-Bunnell (Heterophile) Reaction? Am. J. Clin. Path. **10**:576, 1940.

272. Goldman, L. B.: Hodgkin's Disease: Analysis of Two Hundred and Twelve Cases, J. A. M. A. **114**:1611 (April 27) 1940.

weakness, pruritus and dyspnea. The enlarged glands varied in size and number. At the onset lymphadenopathy was usually unilateral. The spleen was rarely enlarged until late in the course of the disease. Hoarseness occurred in about 6 per cent of the cases. Owing to the rapid enlargement of the mediastinal glands and pressure on the veins, effusion was common. In other types of mediastinal tumors, growth is usually slow and distention of superficial veins is more common. Roentgenograms were considered of little value in the differentiation of the various mediastinal masses.

Involvement of the skin was noted in 38 per cent of the cases. Pruritus, infiltration of the skin and exfoliative dermatitis were most common; only occasionally was herpes zoster present. Bone disease was noted in 6.6 per cent of the cases, and 10 instances of transverse myelitis were found.

It is especially to be noted that there was no characteristic blood picture. Usually there was leukocytosis, with a relative and an absolute increase in granulocytes and monocytes and a corresponding decrease in lymphocytes. Eosinophilia was observed in 20 per cent of the cases. Some degree of anemia was often observed. Fever of the continuous type was most common; the Pel-Ebstein type of fever was rare.

The average duration of life was thirty-two and six-hundredths months. The shortest course observed was two and a half months, and the longest, eleven years. Following treatment, the average duration of life was twenty-three and eight-tenths months. Ten per cent of the patients lived for five years or more.

Baker and Mann [273] reported 65 cases of a condition proved by biopsy or autopsy to be Hodgkin's disease. In 47 cases the patients were males and in 18 females. The disease occurred most often during the second and third decades. In only 1 case was there associated tuberculosis, and the authors state that there is no proved relationship between the two diseases. Adenopathy was observed in every case at some time during the course of the disease, and usually the cervical glands were involved. Splenomegaly occurred in one half of the cases. Fever was not common if only the superficial glands were affected. The average survival period was about eighteen months. Death was often due to associated anemia, pulmonary disease or involvement of the central nervous system.

Levitt and Weisman [274] analyzed 29 cases of Hodgkin's disease. With minor variations, their findings are in agreement with the previously described observations. These authors especially emphasize the value of roentgen therapy and cite figures to prove the prolongation of life with

273. Baker, C., and Mann, W. N.: Hodgkin's Disease, Lancet **1**:23, 1940.

274. Levitt, A., and Weisman, S. J.: Hodgkin's Disease: Case Series Analysis, M. Times, New York **68**:315, 1940.

this type of treatment. If the patients had roentgen therapy the average duration of life was twenty-eight and eight-tenths months; without such treatment the average duration of life was only seven and six-tenths months.

Case reports describing various atypical aspects of Hodgkin's disease are numerous. Lisa [275] cites the case of a 63 year old woman who had associated Raynaud's disease and herpes zoster. Osteopetrosis was observed for the first time by Herscher and Stein.[276] The authors point out that there is probably a hereditary factor, although a definite cause is not known. The disease is characterized by an excessive formation of bone, anemia and fibrosis of the liver, spleen and lymphoid tissue. Cabot case no. *26062* [277] is concerned with the occurrence of Hodgkin's disease involving the retroperitoneal lymphoid tissue and the spleen. Infarction, with subsequent ulceration, of the spleen was observed. Perforation of the stomach resulted from direct contact. Craver and Sunderland [278] cite a case of mistaken diagnosis of carcinoma of the stomach in which this condition had been reported cured by roentgen therapy. Actually the patient had Hodgkin's disease and carcinoma of the colon. Sayago [279] points out that radium is seldom used and reports a case in which the patient was successfully treated with small quantities.

Special cultural technic for the isolation of brucella organisms is described by Poston and Parsons.[280] Employing this method, the investigators cultured glands from 19 patients with Hodgkin's disease. Ten cultures were positive for such organisms. Cultures of tissue from nodes of 3 patients with undulant fever were positive in every instance. From 67 nodes routinely examined, only 1 positive culture was obtained. Wise and Poston [281] demonstrated the coexistence of brucella infection and Hodgkin's disease in 14 consecutive cases by isolation of Brucella

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275. Lisa, J. R.: Neurologic Complications in Hodgkin's Disease, New York State J. Med. **40**:62, 1940.

276. Herscher, H., and Stein, J. J.: Osteopetrosis Associated with Hodgkin's Disease: Review of Literature and Report of Case, Am. J. Roentgenol. **43**:74, 1940.

277. Hodgkin's Disease of Spleen and Retroperitoneal Tissues, Cabot Case 26062, New England J. Med. **222**:233, 1940.

278. Craver, L. F., and Sunderland, D. A.: Hodgkin's Disease and Carcinoma of the Colon: Mistaken Diagnosis of Carcinoma of the Stomach, J. A. M. A. **114**: 1623 (April 27) 1940.

279. Sayago, C.: Radium Therapy in Hodgkin's Disease: Report of Case, Am. J. Roentgenol. **42**:888, 1939.

280. Poston, M. A., and Parsons, P. B.: Isolation of Brucella from Lymph Nodes, J. Infect. Dis. **66**:86, 1940.

281. Wise, N. B., and Poston, M. A.: Coexistence of Brucella Infection and Hodgkin's Disease: Clinical, Bacteriologic and Immunologic Study, J. A. M. A. **115**:1976 (Dec. 7) 1940.

melitensis from cultures of blood or lymph nodes. Apparently the authors used the same data as Poston and Parsons. In summarizing their work, Wise and Poston state that the results do not establish an etiologic relationship of brucella infection to Hodgkin's disease but suggest that the clinical course of Hodgkin's disease may be significantly influenced by brucella infection.

The properties of the encephalopathic agent (the Gordon body) present in the bone marrow of monkeys were investigated by King.[282] He noted that it was readily soluble at a p_H of 7.4, as well as at a lower p_H of 2.0 or 3.0. The point of minimal solubility was a p_H of 4.2. The material was inactivated by a temperature of 75 C. for fifteen minutes; it was digested by pepsin; it had a slight degree of sedimentation with an air-driven centrifuge, and it was nondialyzable. It was precipitated from a solution (p_H of 7.4) by ammonium sulfate, over a range of 0.4 to 0.8 saturation. These findings suggest that the reagent is a protein. This material was injected into guinea pigs, and the clinical and pathologic effects were studied. The latter effects depended on the number of Purkinje cells destroyed.

LYMPHOSARCOMA AND LYMPHOMATOID DISEASES

An extensive review of lymphosarcoma was recently published by Sugarbaker and Craver.[283] They define lymphosarcoma as a malignant neoplastic disease of lymphoid tissue capable of arising in any lymphoid aggregate. It may be acute or chronic and is usually radiosensitive. The outcome is fatal, owing to widespread metastasis. The disease is commonly termed malignant lymphoma, or lymphoblastoma.

Kundrat first recognized lymphosarcoma in 1893. Often it is difficult to classify the disease properly, owing to the varied pathologic manifestations. Two types are recognized, the reticulum type, or lymphosarcoma, and the lymphocytic type, or malignant lymphocytoma. In either there is a predominance of the particular cell, with subsequent obliteration of the follicular architecture, invasion of underlying tissues and outward growth of the tumor (invasion of the capsule and surrounding tissue).

The exact etiologic relations are not known, although the condition is considered to be malignant. Kirschbaum and his associates [284] were able

282. King, L. S.: Some Properties of the Encephalopathic Agent in Primate Bone Marrow (The Gordon Agent), J. Exper. Med. **71**:603, 1940.

283. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: Study of One Hundred and Ninety-Six Cases with Biopsy, J. A. M. A. **115**:17 (July 6); 112 (July 13) 1940.

284. Kirschbaum, A.; Gardner, W. U.; Nahigian, R., and Strong, L. C.: Differentiation Between Sarcomatous and Leukemic Lymphocytes in Mice, Yale J. Biol. & Med. **12**:473, 1940.

to differentiate between sarcomatous and leukemic lymphocytes by injecting the malignant cells into mice. When leukemic cells were injected, regardless of the site or route, there was widespread metastasis, with evidence in the blood stream. When lymphosarcomatous cells were injected under the skin, a localized tumor occurred, without any evidence in the peripheral blood. If cells of the latter type were injected intravenously, there were few "takes." The authors concluded that these results indicated differences in the pathologic processes of the two diseases.

Sugarbaker and Craver point out that lymphosarcoma is less common than Hodgkin's disease, the two occurring in the ratio of 3:4. Males are affected about twice as often as females. The former disease is rare before the age of 20 and after the age of 70, though it has occurred in younger and in older persons. The reticulum cell type predominates.

The initial sites involved, with associated symptoms, in the order of their frequency are lymphoid tissue, the upper respiratory tract, the mediastinum and bone. Cervical glands are usually affected first; then in order of frequency are axillary, inguinal, abdominal, mediastinal and epitrochlear glands. Generalized lymphadenopathy is rare. It is to be noted that during the course of the disease any organ or tissue may be affected.

There is no typical hemogram, and at the onset the blood is surprisingly normal. A definite diagnosis can be made only by biopsy.

Since lymphosarcoma is radiosensitive, roentgen irradiation is the therapeutic method of choice. The disease rarely recurs in the areas treated, although new evidence of it may be found elsewhere. Sugarbaker and Craver divided their cases according to the treatment given. In 49 per cent of the cases roentgen radiation alone was given, in 12 per cent radium or radon, in 13 per cent a combination of roentgen radiation and radium, in 12 per cent surgical treatment and in the remaining cases total irradiation was carried out, according to the method of Heublein. In an analysis of the results obtained with the various types of therapy, it appeared that in the early stages of the disease the combination of surgical treatment and roentgen irradiation was most effective. Later in the course of illness roentgen irradiation alone was the best treatment. The authors demonstrated that the most effective single dose was 400 to 600 and that not over 2,000 to 3,000 r per area should be given.

Of the group of patients that were followed throughout the course of illness, 15.9 per cent had a five year period of survival. In addition to roentgen therapy, other factors which influenced the course of the disease were individual inherent qualities, the extent of the disease on

admission to the hospital, the location of the primary lesion, the age of the patient and the presence or absence of complications.

Owen [285] cites a case of infection with torula which was mistaken for lymphosarcoma. He advises that cultures be made of all material taken for biopsy. From our experience, we are definitely in agreement that fungous infections may clinically simulate lymphoblastoma. It is pointed out by Loveman [286] that lymphosarcoma of the skin may occur long before there is any evidence in the lymph glands. The author emphasizes the importance of making a clinical diagnosis and especially denounces the terminology. A case of leukemia of the skin was reported by Caird [287] as one of chloroma. No true chloroma tumors were found, and from the evidence submitted, the most likely diagnosis is myelogenous leukemia. Lehman and Leaman [288] describe a typical case of Mikulicz' disease occurring in a 55 year old woman. They point out that the disease is benign and should be differentiated from Mikulicz' syndrome, which has a grave prognosis.

Giant follicular lymphadenopathy was first described by Brill, Baehr and Rosenthal, in 1925. As noted by Baggenstoss and Heck,[289] the disease has been recognized more frequently in recent years. These investigators report 13 cases, in 7 of which the patients died. Three necropsies and 8 biopsies were performed. The disease is characterized by an insidious onset, with regional or generalized lymphadenopathy, splenomegaly, normal blood and marked radiosensitivity of the lesions. The average duration of life was four and a half years, though 2 patients survived for seventeen years. The pathologic picture is characteristic, but it is often difficult to distinguish from that of lymphoblastoma or inflammation.

Powell [290] presents 2 cases of giant follicular hyperplasia and recommends roentgen therapy. Salm [291] also describes 2 cases of this disease and expresses the belief that it is a prelymphoblastoma stage. Although

285. Owen, M.: Generalized Cryptococcosis Simulating Hodgkin's Disease, Texas State J. Med. **35**:767, 1940.

286. Loveman, A. B.: Reticulocytoblastoma Cutis (Nonleukemic Malignant Reticulo-Endotheliosis): Report of a Case, Internat. Clin. **4**:163, 1940.

287. Caird, J. C.: Case Record—Chloroma, Edinburgh M. J. **47**:762, 1940.

288. Lehman, J. A., and Leaman, W. G., Jr.: Mikulicz' Disease, Internat. Clin. **3**:105, 1940.

289. Baggenstoss, A. H., and Heck, F. J.: Follicular Lymphoblastoma (Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen), Am. J. M. Sc. **200**: 17, 1940.

290. Powell, C.: Giant Follicular Lymphadenopathy, Canad. M. A. J. **42**:372, 1940.

291. Salm, R.: Two Cases of Follicular Lymphoblastoma, Edinburgh M. J. **47**:486, 1940.

Salm's opinion is in agreement with that of most authors, there are many who consider giant follicular lymphadenopathy to be a benign disease.

LEUKEMIA

Leukemia, according to Jackson,[292] may be defined as an acute or chronic systemic disease involving primarily the blood-forming organs; it is characterized by widespread, disorderly and profitless proliferation of the leukocytes and their precursors, manifest by the presence, often in large numbers, of immature or abnormal white cells in the peripheral blood stream. In the vast majority of cases it leads to death within a comparatively short time. Jackson classifies leukemias in three groups, the myelogenous and lymphatic forms, which may be acute or chronic, and the monocytic form, which is usually acute.

Many interesting observations related to leukemia have been reported by Jackson. In a total of 8,693 autopsies, there were 78 instances of leukemia; of a total of 324,785 patients admitted to the hospital, leukemia was noted in only 333. The disease was more common in men. Acute leukemia was usually seen in younger persons. Chronic myelogenous leukemia was most common in the second and third decades, and lymphatic leukemia occurred in a later age group (45 to 60 years). The patients often exhibited symptoms of increased metabolism and of hemorrhage; negative nitrogen balance was not unusual, and myelophthisic anemia was common. In addition to the blood-forming organs, the areas most often involved were the mouth and pharynx, eyes, central nervous system, skin and bones.

Jackson stated that the onset in acute leukemia is insidious or abrupt, usually occurring in infancy or childhood. The symptoms vary. The signs may be absent at the onset; abnormal white cells are always present in the peripheral blood, although the actual white cell count may be increased or decreased; anemia is always present, and the platelets are decreased. The course is rapidly downhill. Transfusions are only palliative, and roentgen therapy is contraindicated.

Chronic myelogenous leukemia is characterized by an insidious onset, symptoms and signs of increased metabolism, abdominal discomfort, cardiorespiratory symptoms and pain in the left upper quadrant of the abdomen. Physical examination reveals pallor and splenomegaly. The predominant findings in the blood are anemia, abnormal myeloid cells in the circulation and a decreased number of platelets. Treatment recommended includes roentgen irradiation, blood transfusion and administration of solution of potassium arsenite U. S. P.

Chronic lymphatic leukemia is relatively benign. The outstanding sign is generalized lymphadenopathy. The blood picture differs from

292. Jackson, H., Jr.: Leukemias, New England J. Med. **222**:22, 1940.

that in myelogenous leukemia only in that the lymphoid series predominates. Here again, roentgen irradiation and transfusions are suggested as the treatment of choice.

Caird [293] describes 5 cases of leukemia of the acute type, emphasizing the signs and symptoms, and points out that leukopenia is usually present. Stransky and Quintos [294] stress the alterations that occur in the bone marrow of leukemic patients and are of the opinion that these are most important in differentiating the leukemias. Sixteen cases of myeloblastic leukemia are reported by Tischendorf and Herzog.[295] They point out the difficulties encountered in the differential diagnosis and state that the acute and subacute forms of leukemia are variations of the chronic type. It is their opinion that leukemia is a neoplastic disease.

The clinical and hematologic aspects of acute leukemia have been analyzed by Piney.[296] The disease is characterized as fulminating from the onset, more common in males and rare after the second decade. Pallor is severe, and swelling and ulceration of the gums are common, as is fever. Lymphadenopathy and splenomegaly are usually present, although not necessarily so. The course is rapidly downhill, with death occurring in six to eight weeks. According to the author, an atypical form of the disease is frequently observed and can be readily recognized by studies of the bone marrow.

Wintrobe and Mitchell [297] discuss the atypical manifestations which may occur in the various types of leukemia. It is their belief that any and every organ may be involved, whether or not clinical signs are present, and therefore the possibility of the disease must be kept in mind at all times, regardless of the presenting symptoms. These authors are in agreement with the consensus that the study of the bone marrow is most helpful in establishing a diagnosis.

A case of acute eosinophilic leukemia, occurring in a 5 year old boy, is reported by Reye.[298] The patient had a severe anemia, and the differential count revealed more than 70 per cent eosinophils. Death

293. Caird, J. C.: Early Stages of Leukaemia, Edinburgh M. J. **47**:264, 1940.

294. Stransky, E., and Quintos, F. N.: Differential Diagnosis of Leucemia, J. Philippine M. A. **20**:267, 1940.

295. Tischendorf, W., and Herzog, K.: Mehrjährige Beobachtungen über chronische Leukämien und Polycythämien, Deutsches Arch. f. klin. Med. **185**:566, 1940.

296. Piney, A.: Acute Leukemia: A Clinical and Haematological Study, Edinburgh M. J. **47**:616, 1940.

297. Wintrobe, M. M., and Mitchell, D. M.: Atypical Manifestations of Leukaemia, Quart. J. Med. **9**:67, 1940.

298. Reye, D.: Case of Acute Eosinophilic Leuchaemia, M. J. Australia **2**:156, 1940.

was due to cardiac failure resultng from multiple cardiac infarcts. The author was unable to account for the eosinophilia, hence termed the condition "eosinophilic leuchaemia."

Lepak [299] observed a 41 year old man with tuberculosis in whom an enlarged spleen and liver developed, with a blood picture simulating leukemia, the majority of the cells being of the eosinophilic type. In the author's opinion, the diagnosis of eosinophilic or basophilic leukemia is extremely difficult to make, as immature cells of these types are rarely present in the peripheral blood.

The occurrence and frequency of oral manifestations in cases of acute leukemia are stressed by Moloney.[300] Of a series of 152 cases of acute leukemia, oral lesions were present in more than half. The pathologic lesions are mainly limited to the gingival tissues and are characterized by bleeding and infiltration of the gums, which are swollen and painful. Ulcerations and necrosis are commonly present. The author also emphasizes the fact that oral surgical treatment is contraindicated.

Hauptman and Taussig [301] reported a case in which there was infiltration of the female internal genitalia with cells characteristic of leukemia. Although the condition is extremely rare, the authors are of the opinion that this type of neoplastic invasion should always be considered as a possibility in cases of unexplained vaginal bleeding.

Murphy and Brody [302] discuss the occurrence of involvement of the central nervous system in myelogenous leukemia. The usual pathologic manifestation is a localized collection of abnormal white cells in the meninges. Less commonly, there is invasion of the spinal and cranial nerve roots by myeloid elements. A case illustrating the latter type of pathologic lesion is reported by the authors.

The bone changes which may occur in leukemia are classified by Mendl and Saxl [303] as follows: (1) local proliferation in the bone marrow, with erosion of the cellular trabeculae and subsequent forma-

299. Lepak, J. A.: Eosinophilic Hyperleucocytosis: Eosinophilic Leukemia or Myelogenous Leukemia with Case Report with Discussion of Medical Literature, Minnesota Med. **23**:596, 1940.

300. Moloney, W. C.: Clinical Significance of Oral Lesions in Acute Leukemia, New England J. Med. **222**:577, 1940.

301. Hauptman, H., and Taussig, F. J.: Leucemic Infiltration of the Female Internal Genitalia as Cause of Vaginal Bleeding, Am. J. Obst. & Gynec. **39**:70, 1940.

302. Murphy, J. P., and Brody, B. S.: Nerve Root Infiltration in Myelogenous Leukemia, J. A. M. A. **115**:1544 (Nov. 2) 1940.

303. Mendl, K., and Saxl, O.: Bone Changes in Leukemia, Am. J. Roentgenol. **44**:31, 1940.

tion of a central cavity; (2) periosteal proliferation, and (3) sclerosis surrounding the area of cavity formation. Three cases illustrating the bone changes are presented by the authors, who state that roentgenologic evidence alone is not sufficient basis for diagnosing leukemic destruction of bone.

Neal [304] reports the case of a 44 year old man with myelogenous leukemia who died as a result of a ruptured spleen. This complication, the author states, is extremely rare. Another rare complication of myelogenous leukemia, according to Jones,[305] is infiltration of the small intestine. He observed a case in which there was extensive ulceration of the small intestine at the site of infiltration. The ulcer perforated and caused generalized peritonitis.

Bauer and McGavack [306] call attention to the uncommon associaiton of leukemia and diabetes mellitus. Only 16 cases in which the two diseases existed together have been previously reported. They believe that the rarity is due to (1) unreported cases, (2) prevention or modification of the course of diabetes by leukemia, and (3) prevention or modification of the course of leukemia by diabetes.

Blum and Combs [307] observed a case of lymphatic leukemia complicated by pneumococcic pneumonia type III and successfully treated with sulfapyridine and serum. They express the opinion that the drug can be administered to patients with such conditions if it is given with the usual precautions.

Two cases of monocytic leukemia, substantiated by the changes in blood and bone marrow, but not by autopsy observations, were reported by Hsiang.[308] Watkins and Hall [309] observed 29 cases of monocytic leukemia; 23 were of the Nägeli type and 6 of the Schilling type. The authors believe the two types may be differentiated by the characteristics of the predominant cell and its progenitors and by the histopathologic changes in the hematopoietic tissues. In their opinion the Nägeli type

304. Neal, J. M.: Rupture of Spleen in Myelogenous Leukemia, M. Bull. Vet. Admin. **17**:96, 1940.

305. Jones, E. I.: Intestinal Ulceration in Myelogenous Leukemia, Lancet **1**:174, 1940.

306. Bauer, H. G., and McGavack, T. H.: Leukemia and Diabetes Mellitus: Report of Case, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. **3**:7, 1940.

307. Blum, L. L., and Combs, S. R.: Case Report: Chronic Lymphatic Leukemia Complicated by Type III Pneumococcus Pneumonia; Recovery from Pneumonia with Sulfapyridine and Serum, J. Indiana M. A. **33**:424, 1940.

308. Hsiang, H. T.: Acute Monocytic Leukaemia: Report of Two Cases in Chinese, Chinese M. J. **57**:240, 1940.

309. Watkins, C. H., and Hall, B. E.: Monocytic Leukemia of the Naegeli and Schilling Types, Am. J. Clin. Path. **10**:387, 1940.

is a variant of myelogenous leukemia and the Schilling type a variant of leukemic reticuloendotheliosis.

Ulrich and Parks [310] observed a patient with tuberculosis and a leukemoid reaction in the peripheral blood. At autopsy, the bone marrow was leukemic without any evidence of tuberculosis, which, however, was present in other parts of the body. The authors are of the opinion that tuberculosis may be latent and activated by leukemia or may be contracted, as a result of the patient's poor condition.

Aleukemic leukemia is considered by Hynes [311] to be a variant of acute leukemia. He points out that in many ways it may resemble lymphosarcoma leukemia. Hynes cites many cases to illustrate his theory. Bates and Haine [312] describe a case of aleukemic leukemia in a 4 year old boy. The outstanding feature was widespread metastasis, especially in the subcutaneous tissues and muscles. A case of questionable aleukemic leukemia with a duration of life of twenty-five years is reported by Burgess.[313] Sinclair [314] observed a 23 year old woman with aleukemic leukemia. Biopsy of a node revealed the presence of undifferentiated pale cells, which were suggestive of a neoplasm.

Jackson and his colleagues [315] describe a syndrome (agnogenic myeloid metaplasia of the spleen) which simulates leukemia and report 10 cases. The common symptoms were weakness, abdominal distress and hemorrhage. Physical examination revealed splenomegaly. The blood picture was that of a leukemoid reaction. Microscopic sections of the spleen showed marked myeloid metaplasia and scattered foci of immature red and white blood cells and megakaryocytes distributed throughout a slightly or markedly fibrosed spleen. At autopsy, similar ectopic blood formation was present in the liver and the lymph nodes. The bone marrow was variable in consistency, exhibiting at times fibrosis, hyperplasia or aplasia. On some occasions no pathologic change was noted. The authors emphasize the fact that a proper clinical diagnosis must be made in order that no unnecessary treatment be given. According to the cases described by the investigators, roentgen therapy shortens the duration of life.

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310. Ulrich, H., and Parks, H.: The Relation Between Leukemia and Tuberculosis: Report of Case, New England J. Med. **222**:711, 1940.

311. Hynes, M.: Aleukaemic Leukaemia, Quart. J. Med. **9**:177, 1940.

312. Bates, J., and Haine, G. L.: Aleukaemic Lymphadenosis with Extensive Subcutaneous Deposits, Lancet **1**:917, 1940.

313. Burgess, A. M.: Lymphatic Leukemia with "Aleukemic" Stage of Unusually Long Duration, Rhode Island M. J. **23**:26, 1940.

314. Sinclair, C. W.: Aleuchaemic Leuchaemia, M. J. Australia **2**:517, 1940.

315. Jackson, H., Jr.; Parker, F., Jr., and Lemon, H. M.: Agnogenic Myeloid Metaplasia of Spleen: Syndrome Simulating Other More Definite Hematologic Disorders, New England J. Med. **222**:985, 1940.

Kimura and his co-workers [316] report 5 cases of leukanemia, with autopsy observations. It is to be noted that these workers use the term leukanemia to designate a leukemoid blood reaction. A case of acute suppurative pericarditis with an initial leukemoid blood picture in which treatment was successful has been observed by Wolfson and Sharpe.[317]

The configuration of glutamic acid isolated from leukemic tissue proteins was studied by Arnow, Opsahl and Watson.[318] They were unable to detect the presence of any racemic glutamic acid. Turner and his co-workers [319] noted that of 12 cases of myelogenous leukemia the iodine content of the blood was abnormally low in 9 and normal in 3. Of 17 cases of lymphatic leukemia, it was elevated in 41 per cent and normal in 59 per cent. As pointed out by the investigators, there was no overlapping of the two groups.

The treatment of leukemia, generally speaking, is unsatisfactory. According to the "Conferences on Therapy," [320] rest and regulation of activity are indicated; no special diet is necessary, although the patients may have to change their eating habits, owing to pressure symptoms; proper oral hygiene should be maintained; a change of climate is of no value; surgical treatment may be given, with reluctance, under strict supervision; transfusions are only palliative; solution of potassium arsenite U. S. P. and benzene may be helpful, and roentgen irradiation may be beneficial in selected cases. In regard to transfusions, some authorities are of the opinion that they should not be given.

It is to be remembered that roentgen irradiation is only palliative and rarely, if ever, alters the course of the disease. Decision to use roentgen therapy will depend on the white blood cell count, the type of abnormal white blood cells in the circulation and the symptoms and signs present. Roentgen irradiation is contraindicated in cases of acute leukemia, leukopenia (if produced by roentgen rays or drugs), thrombo-

316. Kimura, S.; Hiraga, S., and Kumagai, K.: Five Cases of Acute Myelosis in Childhood, Including Two Cases of So-Called Leukanemia, Tohoku J. Exper. Med. **38**:414, 1940.

317. Wolfson, M., and Sharpe, J. C.: Acute Suppurative Pericarditis with an Initial Leukemoid Blood Picture, California & West. Med. **52**:116, 1940.

318. Arnow, L. E.; Opsahl, J. C., and Watson, C. J.: Configuration of Glutamic Acid Isolated from Subacute Lymphatic Leukemic Tissue Proteins, Proc. Soc. Exper. Biol. & Med. **43**:766, 1940.

319. Turner, K. B.; DeLamater, A., and Province, W. D.: Observations on the Blood Iodine: I. The Blood Iodine in Health, in Thyroid and Cardiorenal Disease and in Leukemia, J. Clin. Investigation **19**:515, 1940.

320. Conferences on Therapy (from Cornell University Medical School and New York Hospital): The Treatment of Blood Disorders; The Use of Transfusions, J. A. M. A. **114**:2375 (June 15) 1940. Roentgen Therapy, ibid. **114**:2451 (June 22) 1940. Conferences on Therapy.[259]

penia and pregnancy. Some investigators recommend large doses; others, small. The treatment may be applied as a spray or locally.

Krebs and Bichel [321] advise that roentgen therapy be given according to the patient's symptoms and that the actual white cell count be disregarded. They state that each patient is an individual problem and should be treated accordingly. Merrill [322] reports 3 cases of leukemia in which uremia developed after roentgen therapy. In his opinion, uric acid metabolism should be carefully studied before and during treatment with roentgen rays to prevent this complication. The combination of transfusions and roentgen irradiation is considered by Corelli and Gaetano [323] to be the most effective treatment. Popp and Watkins [324] state that roentgen therapy is contraindicated in acute myelogenous leukemia, should be administered cautiously in aleukemic myelogenous leukemia and is beneficial in the chronic type.

Barnard and Ross [325] gave large doses of sodium bicarbonate to 2 patients with myelogenous leukemia. They continued the therapy until alkalosis developed. No changes in the hemogram were observed, a result which the authors offer as evidence that neoplastic growth is not related to alkalosis of the tissues.

The phosphorus metabolism of normal and leukemic mice was studied with the aid of radioactive phosphorus by Lawrence and his co-workers.[326] Leukemia was produced in the rats by the injection of malignant cells. The average uptake of phosphorus per gram of whole body weight by bone was only slightly greater in leukemic animals than in normal ones, while the uptake of phosphorus by muscle was slightly less in leukemic than in normal animals. The uptake and exchange of phosphorus in the spleen and lymph nodes were strikingly greater in leukemic animals than in normal ones, although the total phosphorus content of leukemic mice and that of normal mice are approximately the same. In view of these results, as well as the fact that the beta rays

321. Krebs, C., and Bichel, J.: Directions for Roentgenotherapy of Leukoses, Ugesk. f. læger **102**:349, 1940.

322. Merrill, D.: Uremia Following X-Ray Therapy in Leukemia, New England J. Med. **222**:94, 1940.

323. Corelli, F., and Gaetano, M.: Vantaggi delle ripetute modiche transfusioni di sangue nella cura delle leucemie, Riforma med. **56**:167, 1940.

324. Popp, W. C., and Watkins, C. H.: Hematologic Diagnosis and Roentgenologic Treatment of Myelogenous Leukemia, Radiology **34**:663, 1940.

325. Barnard, R. D., and Ross, P. W.: The Effect of Alkalosis on the Blood Picture in Chronic Splenomyelogenous Leucemia, J. Lab. & Clin. Med. **25**:345, 1940.

326. Lawrence, J. H.; Tuttle, L. W.; Scott, K. G., and Connor, C. L.: Studies on Neoplasms with Aid of Radioactive Phosphorus: I. The Total Phosphorus Metabolism of Normal and Leukemic Mice, J. Clin. Investigation **19**:267, 1940.

penetrate only about 1 cm., the authors conclude that radioactive phosphorus may be a good therapeutic agent for treating leukemia.

Lawrence [327] reported 5 cases of leukemia and 2 cases of polycythemia treated by radioactive phosphorus. The substance was administered orally as sodium phosphate in amounts less than a cathartic dose. Conclusions as to the results cannot be drawn, as too few facts are known. It may be said, however, that radioactive substances have the advantage of irradiating the entire body without producing reactions. Warren,[328] also, has used radioactive phosphorus as a therapeutic agent, in 4 cases of leukemia.

Experimental leukemia has added considerable information to the scanty knowledge of this disease. Burchenal [329] studied the relationship of pregnancy to leukemia. Pregnant mice were given intravenous injections of 0.1 cc. of a cell suspension from the spleen of a leukemic mouse. Eighteen females died with leukemia and bore 114 young; 7 mice died with the fetuses in utero; 6 died post partum and lost their young, and the young of 5 other mice that died post partum were raised by foster mothers. In all instances, the fetuses were normal. The offspring died when given injections of a cell suspension from the spleen of a leukemic mouse. The author concludes that mice do not transmit leukemia, that the offspring of leukemic mothers have no immunity and that since the disease did not pass through the placenta, it is not caused by a virus. To substantiate his results, Burchenal cites the literature and states that there is no authentic case in which leukemia was transmitted to the fetus from the mother.

Furth, Barnes and Brower [330] investigated the resistance to transmissible leukemia in mice by means of parabiosis. Three strains of mice were used. Animals of the same sex were joined by suturing the peritoneum, muscles, skin and scapulas. The following experimental combinations were employed: (1) 2 mice susceptible to leukemia (only 1 inoculated); (2) 1 susceptible and 1 resistant mouse (the former inoculated); (3) 1 susceptible and 1 resistant mouse (the latter inoculated), and (4) 1 susceptible and 1 partially resistant mouse (either inoculated). In the first experiment both animals died of leukemia

327. Lawrence, J. H.: Nuclear Physics and Therapy: Preliminary Report on a New Method for Treatment of Leukemia and Polycythemia, Radiology **35**: 51, 1940.

328. Warren, S.: The Treatment of Leukemia by Radio-Active Phosphorus, New England J. Med. **223**:751, 1940.

329. Burchenal, J. H.: Experimental Studies on Relation of Pregnancy to Leukemia, Am. J. Cancer **39**:309, 1940.

330. Furth, O. B.; Barnes, W. A., and Brower, A. B.: Studies on Resistance to Transmissible Leukemia in Mice by Means of Parabiosis, Arch. Path. **29**: 163 (Feb.) 1940.

about the same time and at practically the same stage of the disease. In the second experiment the susceptible mouse died of leukemia, but the resistant animal did not contract the disease. The same results occurred in the third experiment, except that the susceptible animal had a delayed death. In the last experiment, when the partially resistant mouse was inoculated, the nonresistant animal always died and occasionally the partially resistant one did; when the susceptible animal was inoculated, it always died, but in only 1 case did a partially resistant mouse die. As a result of these experiments, the investigators reached the following conclusions: 1. Leukemic cells pass from one susceptible parabiont to the other and produce leukemia in both. 2. The development of leukemia in a susceptible mouse inoculated with leukemic cells is not influenced by its parabiotic union with a resistant mouse, and, further, leukemic cells injected into a resistant mouse may pass to a susceptible parabiont, producing leukemia in the latter without affecting the former. 3. Resistance to transmissible leukemia in mice of a stock only partially resistant to leukemia remains unaltered by parabiosis with susceptible mice. 4. Since the presence of blood vascular anastomosis between parabionts has been demonstrated by the passage of red blood cells and agglutinins from one to the other and since the course of the disease has not been altered, it would appear that transfusions are useless.

BONE MARROW

The importance of studies of the bone marrow as an aid in hematologic diagnosis can no longer be denied. However, many problems related to methods of obtaining marrow, to terminology and to interpretation still exist. Gordon [331] compares the advantages and disadvantages of sternal aspiration and trephining. The former method is rapid, is almost painless and can be repeated often. However, many cells are traumatized, few immature cells are dislodged, there is loss of topographic relationship and an admixture of marrow with peripheral blood occurs. By the trephine method more material can be obtained, the histologic relationship of cells and stroma is preserved and the most immature cells are obtained. The disadvantages of this procedure are that an operating permit is necessary, an open incision is required, the procedure is extremely painful and often it is difficult to identify the cells.

According to Gordon, bone marrow studies are indicated as an aid in the diagnosis of obscure conditions, as a corroborative diagnostic procedure, as a help in the determination of the prognosis and the understanding of the pathogenesis of disease and as a method for the bioassay of specific hematologic agents.

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331. Gordon, H.: Sternal Marrow Biopsy: Methods, Indications and Limitations, Kentucky M. J. **38**:170, 1940.

Wilson [332] is more or less in agreement with the aforementioned advantages and disadvantages and, in addition, states that in obtaining specimens for biopsy there is the risk of infection and hemorrhage.

Bone marrow obtained from 58 autopsy specimens was studied by Jeanneret.[333] The author points out that if the material is obtained within one hour after death it is comparable to living marrow. The polymorphonuclear leukocytes degenerate first and are followed by the myelocytes. The nuclei of the normoblasts undergo pyknosis and fragmentation. Plasma cells, lymphocytes, eosinophils and stroma cells change slowly. Mitotic figures and thrombocytes disappear in one to two hours. The percentage of myeloid cells falls to zero in eight to twenty-four hours. Septic conditions have a noticeable effect on the bone marrow pattern. The author believes that sections of bone marrow are better than aspiration specimens, since the former contain more immature cells and the relationships of their tissues are preserved.

McLean [334] performed sternal puncture on 120 patients with various types of blood dyscrasias. According to his normal standards, the ratio of white blood cells to red blood cells is 6:1. If the mature white cells are omitted, however, the ratio (leukoerythrogenetic ratio) is reduced to 1:4. In pernicious anemia in relapse, the marrow is hyperplastic and megaloblastic; in remission megaloblasts persist but are decreased in number. McLean states that sternal punctures are of no value in the diagnosis of microcytic anemia and are unnecessary in the recognition of leukemia, since the marrow picture is similar to that of the peripheral blood. He further adds that in atypical cases, if other methods fail, sternal aspiration is indicated.

Hyperplastic normoblastic erythropoiesis was observed by Nordenson [335] in cases of pernicious anemia in remission, of hypochromic anemia, of hemolytic jaundice, of erythroblastosis in children, of hemorrhage, of toxic anemia and of anemia associated with digestive disorders. The author points out that degenerative myelopoiesis is diagnostic of pernicious anemia, although megaloblasts may be absent, that lymphatic metaplasia is pathognomonic of lymphadenosis and that increased numbers of megakaryocytes occur in polycythemia and in essential thrombopenic purpura. Monocytic leukemia is characterized by an increase of monocytes in the bone marrow. In myeloma there is a hyperplasia of plasma cells. Typical cells of Gaucher's disease, Niemann-Pick disease and Schüller-Christian disease may be observed in the marrow in cases

332. Wilson, T. E.: Sternal Biopsy, M. J. Australia **1**:405, 1940.

333. Jeanneret, H.: La moelle osseuse en clinique et à la salle d'autopsie. Étude comparative, Schweiz. med. Wchnschr. **70**:351, 1940.

334. McLean, J. A.: Sternal Puncture, M. J. Australia **2**:395, 1940.

335. Nordenson, N. G.: Sternal Puncture and Its Practical Diagnostic and Theoretical Significance, Nord. med. (Hygiea) **6**:834, 1940.

of these conditions. Nordenson also used the aspiration method to study the embryonic development of the various types of blood cells.

The bone marrow in sarcoidosis is described by Lucia and Aggeler.[336] They found that the reactions of the bone marrow were similar to those associated with chronic infection. Limarzi and Schleicher [210] studied the marrow of patients with various types of purpura and hemorrhage. In essential purpura (active phase) the bone marrow showed an increase in the number of megakaryocytes and the presence of many young cells. After splenectomy the bone marrow returned to normal. Hyperplasia of the megakaryocytic tissue was more noticeable in chronic purpura than in the acute form of the disease. In patients with thrombopenic purpura who continued to bleed after splenectomy, the bone marrow appeared abnormal. The marrow in symptomatic purpura was characterized by an increase in megakaryocytes, which was less marked than in the other types of purpura. After hemorrhage intermediary megakaryocytes predominated. The authors conclude that the decreased number of platelets present in the peripheral blood in essential purpura is due to arrested maturation of the megakaryocytes.

Observations on the human sternal bone marrow in cases of hyperthyroid and myxedematous states are reported by Jones.[337] Nucleated cells were increased in conditions of hyperthyroidism and after thyroid therapy in myxedema. In hypothyroidism the number of nucleated cells was decreased as compared with the normal. After thyroidectomy the bone marrow returned to normal. In the author's opinion, the hyperplasia is myeloid in character and is not reflected in the peripheral blood.

Israels [338] recommends the study of the bone marrow in atypical cases of leukemia. Lymphocytosis, which is characteristic of leukemia, may also be seen in infectious mononucleosis and in aplastic anemia. In glandular fever all the other elements of the bone marrow are normal; in aplastic anemia the lymphocytosis is relative and the other cells are normal. Thus the diseases can be easily differentiated. The bone marrow in infectious mononucleosis was also studied by Leitner.[339] The marrow revealed a myelocytic reaction, with interference of cell maturation due to splenic hyperfunction. In the author's opinion, this

336. Lucia, S. P., and Aggeler, P. M.: Sarcoidosis (Boeck), Lymphogranulomatosis Benigna (Schaumann); Observations on the Bone Marrow Obtained by Sternal Puncture, Acta med. Scandinav. **104**:351, 1940.

337. Jones, R. M.: Human Sternal Bone Marrow in Hyperthyroid and Myxedematous States, Am. J. M. Sc. **200**:211, 1940.

338. Israels, M. C. G.: Lymphatic Leukaemia: The Value of Sternal Puncture in the Diagnosis of Atypical Cases, Brit. M. J. **2**:1132, 1939.

339. Leitner, S. J.: Das lymphoidzellige Drüsenfieber (Mononucleosis Infectionsa) mit besonderer Berücksichtigung des Sternalmark-befundes, Schweiz. med. Wchnschr. **70**:117, 1940.

hyperfunction accounts for the leukopenia which often occurs in infectious mononucleosis.

The bone marrow in 6 additional cases of achrestic anemia is described by Israels and Wilkinson.[340] They state that the bone marrow simulates that of pernicious anemia. They add that true megaloblasts do not occur in aplastic anemia; hence the two diseases can be easily differentiated. Morrison and Samwick[341] report a case of aplastic anemia treated by sternal transfusions. In their opinion, the bone marrow was given not as a transplant but because it contains some substance necessary for bone marrow growth. The bone marrow in a case of benzene poisoning was studied by Gray and his co-workers.[342] All the normal elements were reduced.

The presence of an increased number of plasma cells in the bone marrow of patients with multiple myeloma was observed by Haden and Rumsey[343] and King.[344] The bone marrow of patients with various diseases producing myelophthisic anemia was studied by Mettier[345] and by Thompson and Illyne.[346] Tumor cells were observed by Kreyberg and Poppe[347] in the marrow of 8 patients with various types of malignant disease. In their opinion, biopsy sections give more information than sternal aspirations.

According to Ling and his colleagues,[348] culture of the bone marrow is a simple, rational and reliable method for diagnosing typhoid and paratyphoid fever. In a series of 38 cases, cultures of the marrow, blood, urine and stools were made simultaneously. Bone marrow cultures

340. Israels, M. C. G., and Wilkinson, J. F.: New Observations on the Aetiology and Prognosis of Achrestic Anaemia, Quart. J. Med. **9**:163, 1940.

341. Morrison, M., and Samwick, A. A.: Intramedullary (Sternal) Transfusion of Human Bone Marrow: Preliminary Report, J. A. M. A. **115**:1708 (Nov. 16) 1940.

342. Gray, I.; Greenfield, I., and Lederer, M.: Benzene Poisoning: Report of Case with Sternal Marrow Studies, Autohemagglutination and Autopsy, J. A. M. A. **114**:1325 (April 6) 1940

343. Haden, R. L., and Rumsey, J. M.: Multiple Myeloma, or Myelomatosis, M. Clin. North America **24**:369, 1940.

344. King, B. B.: Solitary Plasma Cell Myeloma of Bone as an Initial Stage of Multiple Myeloma, J. A. M. A. **115**:36 (July 6) 1940.

345. Mettier, S. R.: Hematologic Aspects of Space Consuming Lesions of the Bone Marrow (Myelophthisic Anemia), Ann. Int. Med. **14**:436, 1940.

346. Thompson, W. P., and Illyne, C. A.: The Clinical and Hematologic Picture Resulting from Bone Marrow Replacement, M. Clin. North America **24**:841, 1940.

347. Kreyberg, L., and Poppe, E.: Tumor Cells in Sternal Bone Marrow, Lancet **1**:593, 1940.

348. Ling, C. C.; Taur, S. S.; Hsueh, P. C., and Yang, S. Y.: Medulloculture in the Diagnosis of Typhoid and Paratyphoid Fevers: Analysis of Thirty-Eight Cases, Chinese M. J. **57**:11, 1940.

gave the highest percentage of growths during the early and late stages of the disease, and often during convalescence. The growth appeared more rapid and luxuriant in these cultures. In the authors' opinion, it is easier to obtain bone marrow than blood, and therefore culture of the marrow should be routinely employed.

Osgood [349] gives an excellent résumé of his method of culture of human marrow. By this procedure, he was able to study the various effects produced by roentgen rays on marrow cells. From his observations, he suggests that the roentgen rays inhibit mitotic and amitotic division and the cells disappear gradually as they mature and live out their natural life span. Bullowa and his colleagues,[350] employing Osgood's technic, studied the effect of sulfapyridine alone and with serum on pneumococcic pneumonia and on pneumococcus-infected marrow cultures. In marrow cultures, sulfapyridine in a concentration of 5 mg. or more per hundred cubic centimeters leads to ultimate sterility with inoculums of 500 or less per cubic centimeter of types I, II, III or V pneumococci; however, controls uniformly grow out to number over 100,000,000 colonies per cubic centimeter. The larger the initial inoculum, the less likely sulfapyridine will lead to sterility. Sulfapyridine was more effective than sulfanilamide. Specific antiserum appeared to increase the effectiveness of sulfapyridine, although occasionally the reverse occurred. Within definite ranges the higher concentrations of the drug are more effective. Fresher strains of the bacteria are more resistant, and all organisms are not rapidly killed by the drug. In proper doses the drug does not injure the marrow cells, nor does it increase or decrease phagocytosis. The organisms retain their capsule and specificity but often become distorted. Acetyl sulfapyridine is ineffective. Serum from untreated patients with pneumonia is not bactericidal; serum from treated patients has bactericidal properties proportional to the sulfapyridine and antibody content. Administration of the drug alone is followed by a lower death rate than employment of serum alone or of a combination of the two. The lowest mortality rate occurred in cases in which serum and the drug were used in combination in treating the early stages of the disease.

In a similar experiment, Osgood [351] noted the effectiveness of neoarsphenamine, sulfanilamide and sulfapyridine in marrow cultures

349. Osgood, E. E.: Culture of Human Marrow: Summary of Studies to Date, West. J. Surg. **48**:540, 1940.

350. Bullowa, J. G. M.; Osgood, E. E.; Bukantz, S. C., and Brownlee, I. E.: Effect of Sulfapyridine Alone and with Serum on Pneumococcic Pneumonia and on Pneumococcus-Infected Marrow Cultures, Am. J. M. Sc. **199**:364, 1940.

351. Osgood, E. E.: Effectiveness of Neoarsphenamine, Sulfanilamide, Sulfapyridine in Marrow Cultures with Staphylococci and Alpha Streptococci, Proc. Soc. Exper. Biol. & Med. **42**:795, 1939.

inoculated with staphylococci and alpha streptococci. Neoarsphenamine in a concentration of 3 to 9 parts per million was more effective than a 1:10,000 concentration of either sulfanilamide or sulfapyridine and did not significantly damage the marrow cells. The toxic and therapeutic responses of the blood and bone marrow to sulfanilamide were observed by Paul and Limarzi.[352] Nine patients were given 24 to 72.3 Gm. of the drug over a period of eight to seventeen days. Macrocytic anemia was often produced and was accompanied by a normoblastic reaction of the bone marrow. When acute hemolytic anemia occurred, the bone marrow exhibited a more marked reaction, with the presence of younger cells.

Israels,[353] employing a modified technic of Osgood, cultured bone marrow and studied the development of individual strains of white cells. The granulocytes, reproduced by mitosis, had differentiating granules, and their nuclei showed lobulation. Lymphocytes exhibited amitotic division. The monocytes developed into phagocytic cells, and the early forms showed active mitosis.

Higgins and Machella[102] administered sulfanilamide to rats and killed them at various intervals. The effects of the drug on the bone marrow were studied. On the fourth day, a marked myeloid and a mild erythroid stimulation were noted. On the sixth day, if anemia was present, the erythroid stimulation predominated, and this condition persisted after the sixth day regardless of the appearance of anemia. The investigators concluded that the alterations of the leukocytes in the peripheral blood were probably due to nuclear changes produced in the immature white cells in the bone marrow.

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352. Paul, J. T., and Limarzi, L. R.: Toxic and Therapeutic Response of Blood and Bone Marrow to Sulfanilamide, Proc. Soc. Exper. Biol. & Med. **43**: 29, 1940.

353. Israels, M. C. G.: The Culture in Vitro of Leucocytes from Human Bone Marrow, J. Path. & Bact. **50**:145, 1940.

Book Reviews

The Endocrine Function of Iodine. By William Thomas Salter. Price, $3.50. Pp. 351, with 40 illustrations. Cambridge, Mass.: Harvard University Press, 1940.

In this monograph the function of iodine in the endocrine system is correlated with the involved chemical, pathologic and experimental and clinical physiologic aspects. A selective, rather than exhaustive, consideration of the literature on thyroid activity comprises the major part of the book. Using iodine as the common denominator, the author makes an orderly approach to a mass of unorganized data and thereby attains a clearcut statement of clinical and experimental progress in the field.

Considering the author's background, it is neither unexpected nor unwarranted that considerable space is devoted to the special properties and development of knowledge of thyroglobulin. The thyroid-pituitary relationships are considered extensively. Recent advances in determinations of iodine in the blood, including the differentiation of the organic and inorganic forms, are evaluated and discussed. The treatment of the role of the hypothalamus serves to demonstrate the author's liberal approach to the subject of iodine metabolism. In this respect the chapter on iodine and the ovary should be mentioned. The important work being done on iodine balance is reviewed comprehensively. Recent work with radioactive iodine is critically surveyed and interpreted. This presentation is especially provocative to thought, as it tends to supplement and expand the preceding background of the relation of iodine to the physiologic activities of the thyroid gland. A short concluding chapter on clinical problems of thyroid disease is not sufficient to recommend the book for strictly clinical reading. An appendix contains brief statements of methods of chemical and biologic assay and miscellaneous information of interest to the student of thyroid problems. The foregoing factors, along with the excellent cross-indexed bibliography, the complete index and the contemporary data, give the volume the aspect of a handbook on thyroid lore.

The book should prove to be of special value to the student and the investigator of the physiologic relations and the diseases of the thyroid gland; it should aid greatly in orienting the reader to the mass of data produced in this important field of endocrinology in the last ten years; the thoughtful clinician should find it highly stimulating. Lastly, the author demonstrates a new technic in the analysis of an endocrinologic problem.

Obesity and Leanness. By Hugo R. Rony, M.D. Price, $3.75. Pp. 300, with 32 engravings. Philadelphia: Lea & Febiger, 1940.

The increased attention paid to obesity as an important factor in the etiologic and pathogenic relations of many pathologic conditions makes this book particularly appropriate at this time. Much less attention has been paid to leanness, but in this monograph Rony has attempted, successfully, incidentally, to show systematically that these two abnormal conditions of the body are "facets of a single problem."

The first section of the book, some 210 pages, is divided into two parts, the first having to do with the physiologic relations of fats and fatty tissue and the second with the pathogenesis of obesity and of leanness. In this particular section the author deals with the role that is played by caloric intake and output, by the endocrine system and by the nervous system. In the first portion, so far as caloric intake is concerned, he stresses the fact that most fat people have abnormal appetites, whereas the opposite is true of lean persons. He calls attention to the influence of heredity and to the important consideration of body build.

The second section, part III of the book, deals with the clinical aspects of obesity and leanness. These 82 pages include a discussion of the classification and the diagnosis of obesity and of leanness, the clinicopathologic aspects of obesity and the therapy of the two conditions. It was to be expected that in the treatment of obesity the author would condemn the use of dinitrophenol. On the other hand, many pages are devoted to the administration of thyroid, but here also caution is indicated in the use of this drug, as shown by the listing of some eight important contraindications to its use.

While Rony has written primarily for the physician with a good medical education, in the first section of the monograph he lays for the man who is in general practice but is not necessarily trained in any special field a foundation which will permit him to follow intelligently all that comes later. This will make the book available to a large group of readers. Well illustrated, with excellent format, the monograph maintains the high publishing standards which one expects from the company that has brought out the book.

Dermatologic Allergy. By M. B. Sulzberger, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Columbia University College of Physicians and Surgeons. Price, $8.50. Pp. XXII + 540, with 39 illustrations and 13 color plates. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher, 1940.

In the preface to his book the author makes the following statement: "This is not intended to be a book of reference, an encyclopedic treatise on allergy or dermatologic allergy. My objective has not been a presentation for the expert, for the immunologist, the allergist or the dermatologist who is well acquainted with this subject; this book is intended to be only a primer, an introduction to dermatologic allergy, in the form of lectures based on those I have been giving to beginners."

The volume is rather more than the author promises. There are fourteen chapters. Each one represents a well organized lecture and deals with a single phase of a complicated subject. The writing is as simple as possible; particularly clear are the definitions of terms used and the descriptions of technics to be employed. A few select bibliographic references are given at the end of each lecture to whet one's appetite for more knowledge. The illustrations are admirable.

At the end is an interesting appendix, wherein is printed a translation of von Pirquet's article which first made use of the term "allergy." Here, too, are a list of accredited substances useful for patch tests and a short discussion of the proper management of urticarial and eczematous dermatoses.

On the whole, this is an unusually useful primer, if so pretentious a monument of work can be thus regarded. Many students will use it for reference and will consider it as a valuable encyclopedic treatise on dermatologic allergy.

Pharmacology and Therapeutics. By Arthur R. Cushny, M.D., LL.D., F.R.S., late Professor of Materia Medica and Pharmacology in the University of Edinburgh; thoroughly revised by C. W. Edmunds, M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, Mich., and J. A. Gunn, M.D., D.Sc., F.R.C.P., Professor of Pharmacology in the University of Oxford, Oxford, England. Twelfth edition. Price, $6.50, cloth. Pp. 952, illustrated, with 66 engravings. Philadelphia: Lea & Febiger, 1940.

The changes in the twelfth edition of this established text consist primarily in the addition of approximately 50 pages of material concerning new therapeutic agents (sulfanilamide, hormones, vitamins) which have been developed in the four years that have elapsed since the eleventh edition. Complete alteration of the older subject matter has not been attempted, although minor changes have been made. The sketchiness with which some subjects are treated is explained in the prefacial statement, as well as by the further generalization that the constant increase in the scientifically recognized materia medica makes it difficult to combine the

essentials of both experimental pharmacology and therapeutics in 900 pages. Certain "textbook errors" are perpetuated, especially those regarding the actions of drugs on man, errors originally arising from some unwarranted transfer of evidence from experiments on a single animal species.

Considered in its entirety the volume is a good text, the revision reasonably satisfactory and the statements regarding drug action as critical as is to be expected from authors who cannot assume claim to first hand knowledge of all phases of a complicated field.

Magenphysiologie für Röntgenzwecke. By Dr. Med. Habil. G. A. Weltz. Price, 12 marks. Pp. 76, with 62 plates. Leipzig: Georg Thieme, 1940.

In this monograph on the physiology of the stomach, the author presents a series of hypotheses on the function of the stomach. The book is divided into four parts. The first chapter deals with the fundamental laws governing tone and peristalsis. The author enumerates them as follows:

1. Tone is independent of peristalsis. Peristalsis, however, is a function of tone.

2. Peristalsis has a stimulus threshold.

3. The stimulus threshold of peristalsis is dependent on the degree of tone and the increase of pressure.

The second chapter is devoted entirely to tone; the third, to peristalsis and the fourth, to emptying.

The hypotheses are proved by animal experimentation as well as clinical roentgenologic studies. The author makes good use of roentgen kymography. The monograph includes a neat device which enables the reader to restore motion to the kymographic illustrations.

In the preface Dr. Weltz expresses the hope that he will provide a stimulus for further research in normal and abnormal gastric physiology. I believe he has ably succeeded. This book is worthy of careful study by the pure physiologist as well as the roentgenologist.

Diseases of the Digestive System. By Eugene Rosenthal, M.D. Price, $8.50. Pp. 394, with 234 illustrations. St. Louis: The C. V. Mosby Company, 1940.

This book is the most profusely illustrated medical text that the reviewer has yet seen. The author states that by the use of the many labeled and multicolored diagrams the student is enabled to obtain an association of ideas in every case. There is no question that the use of these illustrations will be a great help to those persons who have a good visual memory. Most of the diagrams are simple and quickly understood, while others, such as the one on page 347, are more intricate.

The discussion of the various diseases is done in an orderly and fairly complete manner, although in some instances, the dysenteries for example, the handling is sketchy.

In dealing with therapy, the author employs freely the proprietary names of various drugs which are not generally used in this country. There is, among other things, no reference to vitamin K in the discussion of the treatment of obstructive jaundice, and the use of the Miller-Abbott tube in cases of intestinal obstruction is not mentioned.

The book, because of its novel arrangement, is interesting to read; the printing is excellent and the binding is good.

Manual of Medical and Surgical Emergencies. Edited by J. C. Geiger, M.D., Director, Department of Public Health, City and County of San Francisco. Price, $2.50. Pp. X + 199. San Francisco: J. W. Stacey, Inc., 1940.

Not long ago a farmer in the western part of California wrote to the medical school for advice. It appeared that rattlesnakes were invading his territory and he wished to know what to do if any of his people were bitten. He said that the doctors in his part of the world appeared to know peculiarly little of such matters.

This manual will be useful to all physicians who are forced to meet medical emergencies of any sort. It has been compiled by a group of experts who know of what they write. It is well indexed and is written so simply and clearly that when a sudden juncture demanding immediate medical action occurs, this manual can be pulled from the shelf and referred to, and by its advice, without delay, can make possible intelligent, expert management.

The subject matter included in the book covers a wide range of possibilities: from the care of abdominal emergencies through the entire alphabet of accidents, down to how to treat wounds from a wringer or x-ray burns. Every hospital library should have copies at hand which the interns can get at; even the specialist serenely at work in his office may be glad of a copy in his library when the Black Widow caresses him.

A Textbook of Medicine. By American authors. Edited by Russell L. Cecil. Fifth edition. Price, $9.50. Pp. 1744, with 173 illustrations. Philadelphia and London: W. B. Saunders Company, 1940.

The new fifth edition of Cecil's "Textbook of Medicine" seems to establish the book definitely as one of the institutions of American medicine. Compressed into relatively brief space one finds a miniature system with concise but authoritative articles by men whose names for the most part are outstanding in their fields. It would take too much space to discuss individual sections, but the editor is to be congratulated on the character of the present revision, in which a good many articles have been entirely rewritten, sometimes by a new man. While a book of this sort lacks in a sense the homogeneous viewpoint of a single writer, it must be admitted, even if with regret, that no one man can any longer cover the subject with authority. The reviewer finds himself constantly using Cecil for rapid reference, and usually with satisfaction.

Annual Review of Physiology. By J. Murray Luck and Victor E. Hall. Vol. II. Price, $5. Pp. 501. Stanford University P. O., Calif.: American Physiological Society and Annual Reviews, Inc., 1940.

In volume II of the "Annual Review of Physiology" the tradition so well established by volume I is continued. The twenty reviews cover, among other things, such important subjects as peripheral circulation, the heart, endocrine glands, special senses and blood. As in last year's volume, the material is tremendously condensed and really furnishes a key to the large bibliographies which follow each article. Every physician who wishes to keep up with the role of physiology in medicine needs this book.

Organismen und Umwelt. By R. Otto, K. Felix and F. Linke. Price, 15 marks. Pp. 275, with 67 illustrations. Dresden and Leipzig: Theodor Steinkopff, 1939.

This paper-bound volume contains the transactions of the second scientific conference held at Frankfort on the Main, Germany, in June 1939. It is composed of twenty papers which deal with a great variety of subjects in the field of medicine and allied sciences. Most of the papers are supplemented by discussions. Since the contributors come from many European nations, this volume gives one an interesting insight into continental thought on these subjects.

Food, Nutrition and Health. By E. V. McCollum and J. E. Becker. Price, $1.50. Pp. 127. Baltimore: The Lord Baltimore Press, 1940.

This little book, written by seasoned authorities in the field, gives in a small space a great amount of information about food and vitamins. After discussing the needs of the normal diet, the authors present interesting chapters on the relation of diet to the teeth, to pregnancy and the like. The reviewer has only one minor criticism: At times the discussion is a little too deep for the average layman.

Die Geschichte der Schwindsucht. By Dr. Richard Bochalli. Price, 4.30 marks. Pp. 73. Leipzig: Georg Thieme, 1940.

This booklet of 73 pages deals with what was called phthisis before the time of Bichat, and it is evident that the term includes tuberculosis of the lungs, to the history of which a second volume will be devoted.

The author does not avoid the danger of overemphasizing the merits of our great medical forebears, particularly in the field of therapy. This is a rather prevalent error in such treatises. Another individual error is the author's reference to passive motion when a patient is carried in a chair or other conveyance. It is perfectly true that this is passive motion, but it is not the kind of passive motion generally understood in medicine.

Even if the author does not seem a profound student or always a clear thinker, the monograph may be perused with some profit.

Complete Guide for the Deafened. By A. F. Niemoeller. Price, $3. Pp. 256. New York: The Harvest House, 1940.

Handbook of Hearing Aids. By A. F. Niemoeller. Price, $3. Pp. 156. New York: The Harvest House, 1940.

These two little books seem to the reviewer who is not an expert in the subjects involved to cover them adequately and in an interesting way. In the guide for the deafened the short chapters dealing concisely with every phase of deafness, including lip reading and the psychologic problems of the hard of hearing, seem especially useful.

Psychotherapy. By Lewellys F. Barker. Price, $2. Pp. 218. New York: D. Appleton-Century, 1940.

Most physicians reading psychiatric literature soon become lost in a morass of terminology and are unable to make much sense out of the technical material. Dr. Barker's little book gives to the reader not specially trained in psychiatry a concise and stimulating account of the methods and results of dealing with the common psychoneuroses encountered by the physician in general practice. The authoritative touch is evident throughout; probably no one in the country has better results in practice with the neurotic patient than does Dr. Barker. An interesting bibliography is appended.

Diseases Transmitted from Animals to Man. By Thomas G. Hull. Second edition. Price, $5.50. Pp. 403, with 45 illustrations and 55 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

It is an interesting sidelight on modern specialization that the editor of this book, which deals with only a part of the field of infection, felt the need of no less than fourteen collaborators. It is the good fortune of the reader, however, to gain the authoritative discussions of these experts. All the important diseases which may be transmitted to man from animals are described. Most of the articles stress epidemiologic aspects, and in some cases the clinical descriptions are perhaps too brief, for instance, that of botulism. The recently developed prophylaxis of tetanus by toxoid is also barely mentioned. Such few shortcomings are, however, more than balanced by the general high quality of the book, the excellent illustrations, the instructive diagrams and the attractive format.

The 1940 Year Book of Pathology and Immunology. By Howard T. Karsner and Sanford B. Hooker. Price, $3. Pp. 688, with 115 illustrations. Chicago: The Year Book Publishers, 1940.

The Year Book Series has been so successful that the idea of a volume on pathology and immunology seems in order. Under the editorship of Dr. Karsner and Dr. Hooker a most attractive volume has been produced. The material does not lend itself to review because it is a series of abstracts of articles, but here in compact form one finds boiled down several hundred of the most important contributions of the year. The volume should be of great use to pathologists, to bacteriologists and to physicians in general.

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